Monoclonal Antibodies as Promising Therapeutic Agents in the Pharmaceutical Industry and Their Current Challenges

By

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STUDENT DECLARATION

I hereby confirm that this dissertation titled *"Monoclonal Antibodies as Promising Therapeutic Agents in the Pharmaceutical Industry"*, which is presented in partial fulfilment of the requirements for the award of the MSc in Pharmaceutical Business and Technology, represents my original work, under the supervision of Dr. Munira Derby.

I have appropriately indicated all sources used in the preparation of this study through accurate referencing. I also verify that I have neither copied nor plagiarised the work of anyone else.

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Date: 28.08.2020	Date: 28.08.2020

TABLE OF CONTENTS

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ABSTRACT

Monoclonal antibody discovery and their use as therapeutic agents have made a revolutionary transformation in the research focus of the pharmaceutical industry which reflected to market growth with their promising profile for considerably severe diseases which are lacking in a complete treatment such as cancer and autoimmune disorders. However, their biochemical aspects bring various complexity and challenges in the development and use. This study evaluates the impact that monoclonal antibody therapeutics have made on the pharmaceutical industry, identifies the success in the generation of different monoclonal antibody formats over time, finds out the current bottlenecks within the development and therapeutic use of monoclonal antibodies, and assesses their potential as therapeutic agents for currently untreatable diseases, with a special emphasis on their promising implementation into COVID-19. The study comprises qualitative and quantitative approach and was carried out with a group of 98 professionals that consisted of scientists, medical doctors, regulatory professionals, pharmaceutical/biotechnology professionals. Findings show that the most challenging factor in the development of monoclonal antibody therapeutics is the drug design and formulation, while high costs was identified as the most challenging factor for their use. Even though the bottlenecks in the development and use of monoclonal antibodies, challenges are considered manageable in the close future as a consequence of the growing interest in improving monoclonal antibodies, and global focus for their use against COVID-19, as well as patent expirations which will lead to biosimilar alternatives.

Key words: Antibodies; monoclonal antibodies; chimerization technology; hybridoma technology; cytokines; COVID-19.

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ADCs	Antibody-drug conjugates
AML	Acute myeloid leukemia
Anti-IL-6R	Anti-interleukin-6 receptor
BARDA	Biomedical Advanced Research and Development Authority
BIRAC	Biotechnology Industry Research Assistance Council
CD19	Cluster of differentiation 19
CD20	Cluster of differentiation 20
CD3	Cluster of differentiation 3
CDSCO	Central Drugs Standard Control Organisation
COVID-19	Coronavirus disease 19
CRUK	Cancer Research UK
DBT	Department of Biotechnology
DFG	German Research Foundation
DST	The Department of Science and Technology
EpCAM	Epithelial cell adhesion molecule
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HGS	Human Genome Sciences
ICMR	Indian Council of Medical Research
IDA	Industrial Development Authority
IL-6	Interleukin 6
NHPs	Non-human primates
NIH	National Institutes of Health
RA	rheumatoid arthritis
SARS-Cov2	Severe acute respiratory syndrome coronavirus 2
SFI	Science Foundation Ireland
SGK	Turkish Social Security Agency
TNF	tumour necrosis factor
TNF- α	tumour necrosis factor alpha
TUBITAK	The Scientific and Technological Research Council of Turkey
TUSEB	Health Institutes of Turkey

UCD	University College Dublin
WHO	World Health Organization

CHAPTER I: INTRODUCTION

1.1. Background of the Study

Monoclonal antibodies are considered very likely to be hope for rapidly growing severe diseases that for the most part end up with lethality. According to Ipsos, a multinational market research company, the most common cause of death in 2019 in global was cardiovascular diseases (32%), followed by cancer (24%), neurological disorders (9%), lower respiratory infections such as pneumonia (6%), chronic respiratory diseases such as asthma (5%), diabetes and kidney diseases (5%) of which the use of monoclonal antibody therapeutics is emerging for their treatment (Nissim and Chernajovsky, 2008; Ipsos, 2020). Additionally, there are ongoing pre-clinical and clinical studies about the use of monoclonal antibodies for the COVID-19 pandemic that arose in Wuhan, China in December 2019 and hit over 24 million people in global, resulting in over 833,000 death by August 27, 2020.

Because of the high market demand and promising aspects, many of the leading pharmaceutical companies have begun to invest in the research and development of monoclonal antibody therapeutics, launched new antibody generation techniques for a stronger efficacy, better quality and safety of the product, also to expand their use to make them available for the treatment of more diseases with no cure. The use of monoclonal antibody therapeutics is rapidly growing in global and believed to be the future of the pharmaceutical industry (Lu *et al.*, 2020).

1.2. Statement of the Problem

The collaboration between scientists, medical doctors, and the pharmaceutical industry has a common purpose: to provide the safest, most efficient, highest of quality, and cost-effective treatment in the fastest time to make the treatment accessible to every patient in need, aiming to improve human health and life quality of patients. However, the circumstances may not be as ideal as stated, thus, it may not always be possible to achieve all of those aspects at the same time. For instance, even though monoclonal antibody therapeutics has made an impressive impact on the pharmaceutical industry, there are still bottlenecks remained regarding the development process and their therapeutic use (Santos *et al.*, 2018).

To be more specific, the technology and methods utilised to generate monoclonal antibodies are highly expensive, time-consuming, and difficult to achieve. Because the therapeutic use of monoclonal antibodies is relatively new and still continues to be improved, a huge investment on research and development is needed to overcome their challenging aspects (Sewell *et al.*, 2017; Almagro *et al.*, 2018).

Research and development studies cost billions for many biologics/monoclonal antibody therapeutics, which constitutes the main challenge. In addition to that, their production expenses are also high as they are manufactured in small amounts by using advanced biotechnology techniques. Along with their high expenses in research and development, and manufacturing, another element that increases the cost of monoclonal antibody therapeutics is that very less number of approved biosimilar alternatives (Wu *et al.*, 2018).

1.3. Purpose of the Study

The purpose of this study is to evaluate the therapeutic use and the potential of monoclonal antibodies as an emerging technology in the pharmaceutical industry, and identify their current challenges in the development and therapeutics use considering the perspectives of scientists, medical doctors and pharmaceutical/biotechnology professionals.

1.4. Research Objectives

Objective 1: Assessment of the progression of monoclonal antibody generation over time to provide better quality, safety and efficiency of the product and advance its therapeutic use.

Objective 2: Identification of the current challenges in the development and therapeutic use of monoclonal antibody therapeutics.

Objective 3: Analysis of the therapeutic use and challenges of monoclonal antibodies from different perspectives of professionals.

Objective 4: Evaluation of the potential of monoclonal antibodies for the treatment of recently emerged COVID-19 pandemic.

1.5. Research Questions

- How did monoclonal antibody therapeutics impact the market profile and investments of the pharmaceutical companies?
- How have monoclonal antibody generation been improved since the discovery to assure the quality, safety and efficiency of the product and advance the therapeutic use?
- What are the challenges in the development of monoclonal antibody therapeutics?
- What are the viewpoints of professionals with different scientific backgrounds about monoclonal antibody therapeutics in terms of their use and challenges?
- How urgent is the need of treatments of the diseases in which monoclonal antibodies show promise?

1.6. Scope and Limitation of the Study

This study covers the impact of monoclonal antibodies on the pharmaceutical market, the progress of monoclonal antibody types over time, the challenges in the development and therapeutic use of monoclonal antibodies from different perspectives of scientists, medical doctors, regulatory professionals, and pharmaceutical/biotechnology professionals, and their potential for the treatment of Coronavirus disease 19 (COVID-19).

The scope of this study does not cover:

- The use of monoclonal antibodies for diagnostic purposes.
- The regulations for biological products/biosimilars.

1.7. Outline of the Dissertation

The dissertation comprises of six chapters which initiates with a brief introduction in Chapter I, where the background of the study is explained, the problem is explained, purpose of the study is provided, research objectives and questions are presented, along with the scope and delimitation of the study and the significance.

Chapter II comprises of literature review, which begins with a short introduction about the transformation of the pharmaceuticals into biologics, continues with the monoclonal antibody market and further continues with monoclonal antibodies. Their therapeutic applications, importance, discovery, progress over time, challenges in the

development and therapeutic use and ends with their potential implementation into COVID-19.

Research methodology is presented in Chapter III, which includes the explanation of the research philosophies and further strategies that this study followed. The data obtained from primary and secondary research are presented under Chapter IV and discussed in Chapter V.

According to the obtained results, the findings were concluded, and possible recommendations were presented in Chapter VI.

1.8. Significance of the Study

The identification of the difficulties in the development and therapeutic use of monoclonal antibodies and focusing on the most impactful element on the process are the first steps to overcome these problems.

The considerations from the experts in the monoclonal antibody field plays a crucial role for the biotechnology industry as the problem can be effectively solved with the collaboration between scientists; who are keys in research and development of therapeutics and experts in understanding of disease mechanisms, medical doctors; who witness to the clinical use of drugs in the first place, which makes them well aware of any possible complication during the treatment, and the pharmaceutical industry; in which their progress depends on the outcomes of the patients, scientists, and health care professionals primarily.

Considering that, this study provides specific attention to the perspectives of scientific, medical, regulatory, pharmaceutical/biopharmaceutical professionals about the challenges in the development and therapeutic use concerning monoclonal antibody therapeutics. Additionally, the promising aspects of monoclonal antibodies in the pharmaceutical industry, and their potential implementation into the recently emerged COVID-19 pandemic is also included in this study. While the treatment for the pandemic is urgently needed in the world, the potential of monoclonal antibodies as possible cure to COVID-19 is highly important (Guaraldi *et al.*, 2020).

CHAPTER II: LITERATURE REVIEW

2.1. The Transformation of the Pharmaceuticals from Conventional Medicine into Biologics

The pharmaceuticals have been reshaped over the past two decades with the launch of protein-based medicines, also referred as “biologics”. They can consist of proteins, nucleic acids, sugars, also combination of these biological materials, or even living entities such as cells and tissues (Shepard *et al.*, 2017). With the advancements in the genetic engineering techniques, biological products can include gene therapy, recombinant proteins, hormones, or vaccines and blood components such as antibodies. They are manufactured by isolating from the natural sources – human, animal, or microorganism, or by using biotechnology techniques and other cutting-edge technologies which shows promise to overcome medical needs that currently have no solution (FDA, 2019).

Contrary to conventional medicines, also referred as small molecules, which are chemically manufactured with well-known structure, biological products are complex molecules that are not certainly identified and characterized. They are susceptible to heat and carry the risk of microbial contamination (FDA, 2019).

Monoclonal antibody therapeutics constitutes the majority of biological products (Shepard *et al.*, 2017). They have even more complex molecular structure than many other biologics, therefore, they are produced using the most advanced technologies (Mabxience, 2019).

Figure 2.1. shows the degree of complexity between small molecule as conventional treatment method, biological product, and monoclonal antibody structure.

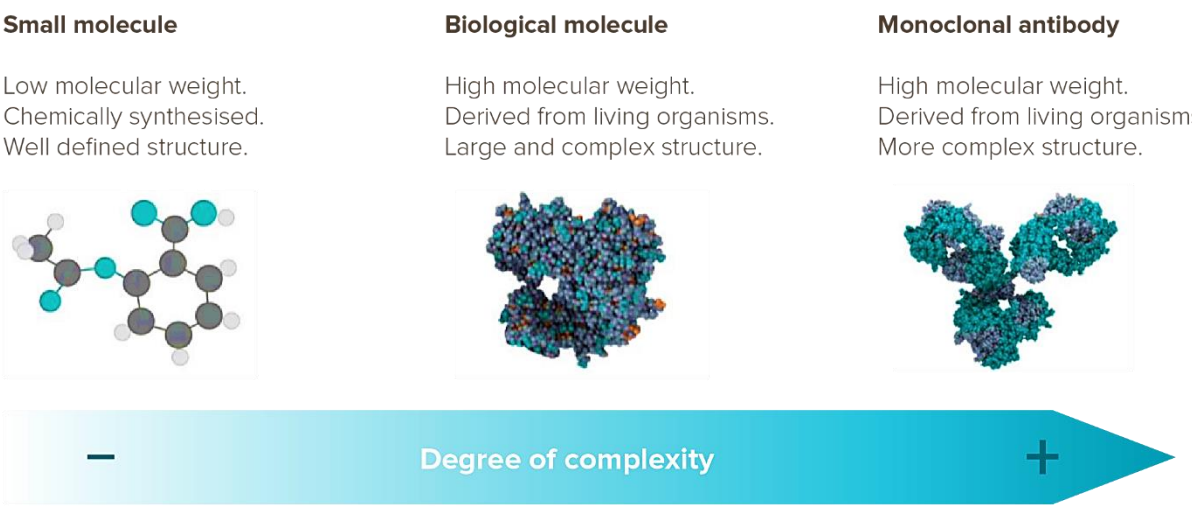

Fig. 2.1. The degree of complexity between conventional treatment method, biological product, and monoclonal antibody structure (Mabxience, 2019).

2.2. An Overview of Monoclonal Antibody Therapeutics

Monoclonal antibodies have a wide range of therapeutic applications varying from different types of cancer disease and autoimmune disorders such as rheumatoid arthritis, lymphoma, Crohn's disease, psoriasis, as well as organ transplantation (Da *et al.*, 2017; Mabxience, 2019).

Cytokines are proteins that are responsible for activating the human immune system in the event of infection. However, the overproduction of these molecules results to cytokine storms which are an important risk factor of autoimmune disorders (NRAS, 2020). There are more than 100 immune-mediated diseases of which 7% of the global population is affected and statistics show that 75% of the patients are women and 25% of them men (AARDA, 2016; OWH, 2017).

Figure 2.2. shows the cytokine types (interleukine-1, interleukine-6, interleukine-17, tumour necrosis factor-α) that cause autoimmune disorders. Demonstration of cytokine storms is provided in Figure 2.3.

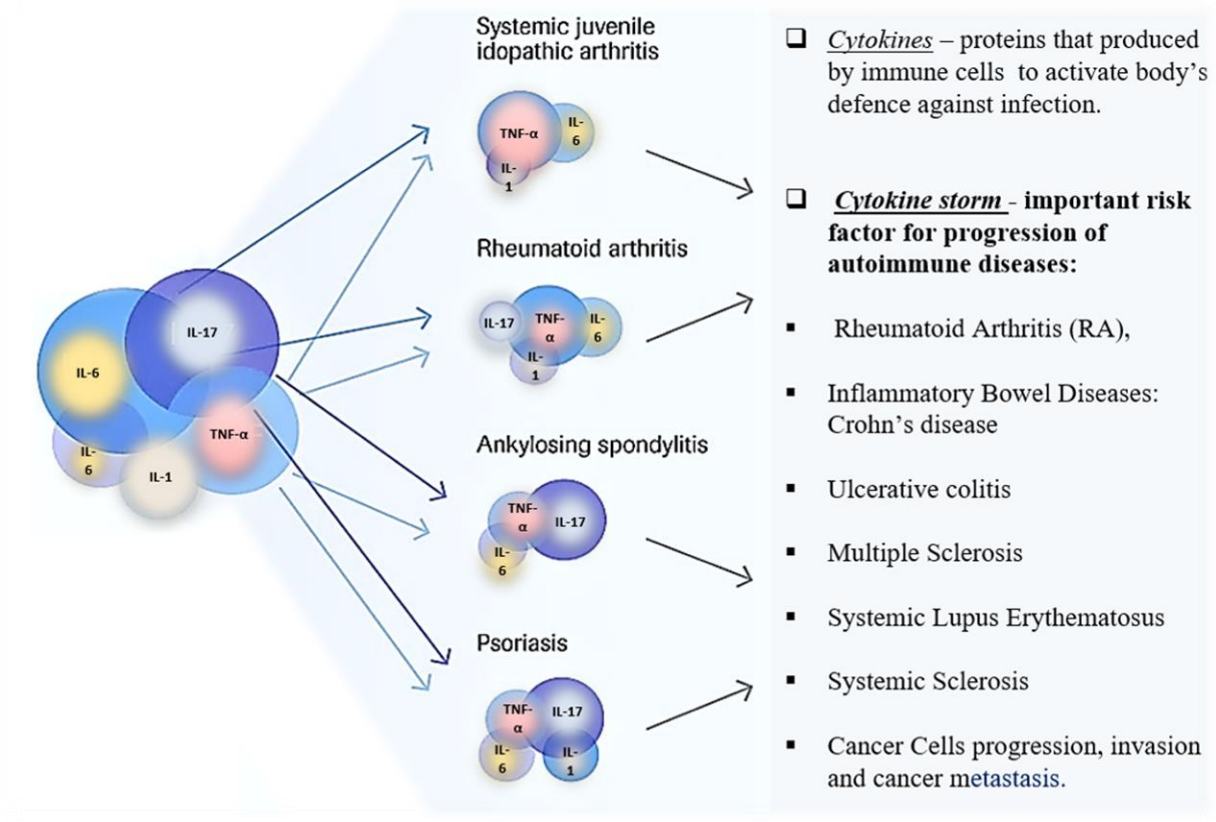

Fig. 2.2. The cytokine types that cause autoimmune disorders (Luo et al., 2020).

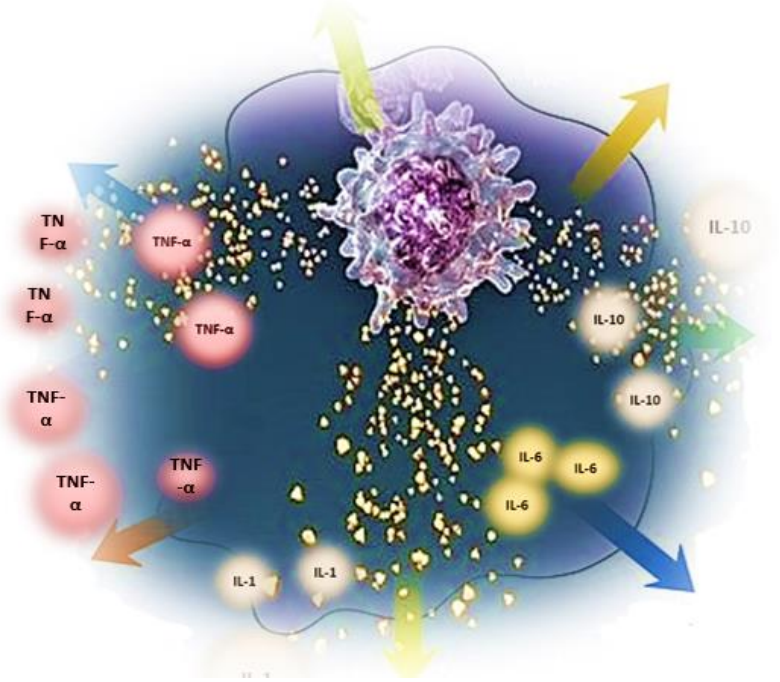

Fig. 2.3. Demonstration of cytokine storms (Luo et al., 2020).

Monoclonal antibodies act against these cytokines to reduce their existence and activity in the body by neutralizing cytokines directly, or by binding their receptors which would block the interaction between them (NRAS, 2020). These cytokine blocking monoclonal antibodies have made a revolution in therapeutic approaches, together with bringing quite considerable profits to the pharmaceutical industry. Remicade (infliximab), Simponi (golimumab), Cimzia (certolizumab pegol), and Humira (adalimumab) are examples to approved monoclonal antibodies that inhibit the effect of cytokines (Shepard *et al.*, 2017; NRAS, 2020).

Additionally, the studies on cytokine blocking monoclonal antibodies have also gained pace because of COVID-19 as cytokine storms in exceeding amounts were detected in patients with severe conditions (Luo et al., 2020).

2.3. The Monoclonal Antibody Market

Over the past 30 years, monoclonal antibody-based drugs have switched from being a research target to a developed technology and taken place in clinical research to even commercialization. Throughout the last 5 years, monoclonal antibodies have been the fastest growing segment in global biopharmaceutical market and kept their blockbusting place in the pharmaceutical market. (Lu *et al.*, 2020).

In the worldwide best-selling drug portfolio of 2018, 8 drugs out of 10 were biological medicines. In the same year, the global market capitalization of monoclonal antibodies was at US$115.2 billion, while the forecast for 2019 was $158 billion and it is expected to grow up to $300 billion by 2025. Therefore, the market for therapeutic antibody medicines has massively grown as new medicines have been authorized in the treatment of several human ailments, such as autoimmune, infectious, metabolic diseases as well as many cancer types. There have been 182 monoclonal antibody-based drugs proceeding with the Phase III clinical trials throughout the world since April 2019. The number of US FDA approved therapeutic mAbs was 79 as of the end of 2019, and yet it is expected to increase massively (RIC, 2019; Lu *et al.*, 2020).

The major pharmaceutical companies leading the monoclonal antibody market are followed as Merck, Roche, AbbVie, Johnson & Johnson, Novartis, and Amgen. Humira by AbbVie, Avastin and Rituxan by Roche, Keytruda by Merck, Remicade and Stelara by

Johnson & Johnson, Enbrel by Amgen were the best-selling eight monoclonal antibody drugs in 2018 that made US$64 billion together with a collective 55,6% share in global market (RIC, 2019).

The current and estimated market growth of monoclonal antibodies are shown in Figure 2.4. Additionally, the best-selling 10 monoclonal antibody therapeutics in 2018 are shown in Figure 2.5.

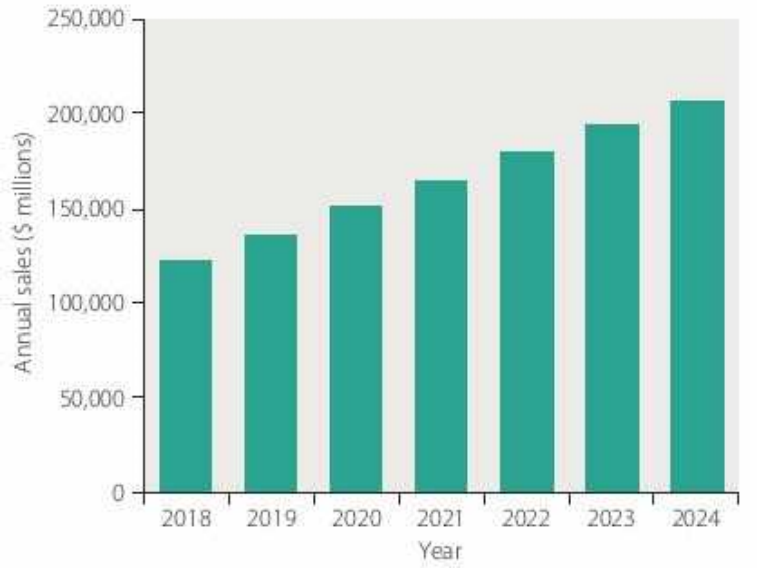

Fig. 2.4. The market growth of monoclonal antibody therapeutics and their estimated annual sales by 2024 (BioPharma, 2019).

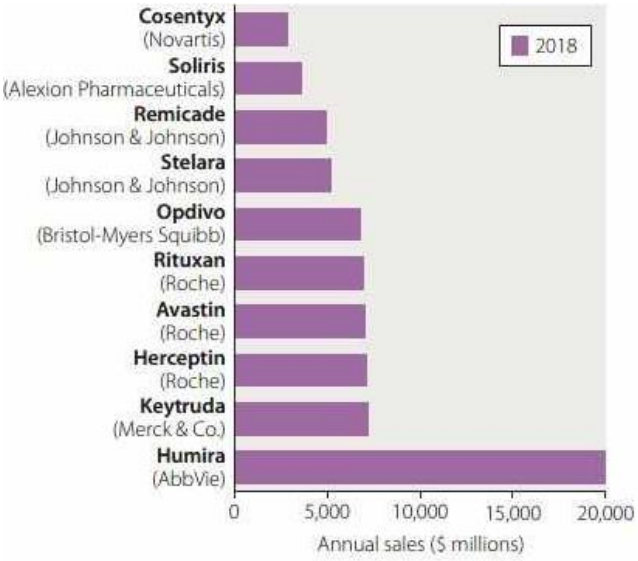

Fig. 2.5. The best-selling 10 monoclonal antibody therapeutics in 2018 (BioPharma, 2019).

2.4. The Importance of Monoclonal Antibodies

Antibodies are the fundamental functional unit of the humoral immune system, as they are produced in order to neutralize toxins, inhibit the activity of foreign materials which are referred as antigens (Hanack *et al.*, 2016; Mahmuda *et al.*, 2017). They are synthesized and secreted by B-cells as an immune response against antigens such as fungi, bacteria, viruses, toxins, etc (Stewart, 2004; Forthal, 2014; Zahavi *et al.*, 2018) and can be categorized as polyclonal and monoclonal. Monoclonal antibodies are synthesized in laboratory conditions by replicas originated from a single parent B-cell (NIH, 2020). They show a robust affinity to one particular region of an antigen that antibodies bind to. Polyclonal antibodies on the other hand, are generated by various clones of B-cells and can bind to diverse regions in the same antigen (NICB, 2016; Hanack *et al.*, 2016; Panawala, 2017; Sathyajith, 2020).

The main aspects of monoclonal antibodies that make them unique are:

- Batch-to-batch uniformity,
- Low background reactivity,
- Uniqueness to a single epitope,
- Potential to be produced identically and in large amounts at a time,
- Providing higher accuracy in assays that require quantification of the protein levels.

These aspects reduce the risk of cross-reactivity and allow monoclonal antibodies to have a highly homogenous population. Thus, they provide better results in experiments and can be used to target specific antigens. Being able to be produced in larger quantities is another advantage for diagnostic manufacturing and therapeutic drug development (Panawala, 2017).

Before the discovery of hybridoma technology, scientists were dependent on polyclonal antibodies for experiments concerning the particular proteins of interest within complex biological environments to be identified and quantified. However, even though polyclonal antibodies have their individual set of advantages, they are not convenient to be applied for *in vivo* experiments or therapeutics because they cannot provide batch-to-batch consistency and they possess high amount of background reactivity (Zaroff and Tan, 2019). Monoclonal antibodies are a much better solution for the therapeutic drug development as it

requires large quantities of identical antibody unique to one single epitope. For common research purposes instead, polyclonal antibodies are usually preferred. To give an example, when used for affinity purification of serum against small antigen targets, the benefits of polyclonal antibodies outweigh what monoclonal antibodies provide (Panawala, 2017).

2.5. Therapeutic Applications of Monoclonal Antibodies

The highly specific identification and attachment ability of monoclonal antibodies for many molecules has been broadly used for the detection of cytokines, vitamins, allergens, hormones, many tumour markers in the field of diagnosis, and an extensive variety of indicators linked with many diseases, as well as microbial infections (Da *et al.*, 2017). These aspects allowed monoclonal antibodies to be used for clinical diagnosis, therapeutic targets, delivery of other drugs, and identification of markers.

Medical application of monoclonal antibodies has turned out to be a crucial element of therapies in numerous diseases including cardiovascular, autoimmune, oncology, infectious diseases as well as organ transplantation (Nissim and Chernajovsky, 2008). In addition to these, they can be used for osteoporosis, age-dependent macular degeneration, multiple sclerosis, asthma, too. The investigation of possible use of monoclonal antibodies in the treatment of metabolic diseases, central nervous system disorders and the prevention of migraines is ongoing (Da *et al.*, 2017).

2.6. The Discovery of Monoclonal Antibodies by Using Hybridoma Technology

During the 1890s, Emil von Behring and Kitasato Shibasaburo noticed that animals which have never been infected with diseases such as diphtheria or tetanus before, could gain immunity by blood taken from animals which formerly exposed to such diseases. Subsequent to that, it was discovered by Paul Ehrlich that the defence in blood sourced by antibodies (Kaufmann, 2017).

Along with these findings, antibodies have been considered as potential magic bullets for human health and thus scientists focused on possible ways to separate and purify specific antibodies from the billions generated by the immune system. The first study on the production of mouse-sourced monoclonal antibodies was completed with hybridoma technology by Georges Köhler and Cesar Milstein in 1975 based at the Laboratory of Molecular Biology in Cambridge, UK (Nissim and Chernajovsky, 2008). The discovery of

hybridoma technology made Milstein and Köhler share the Nobel Prize for Medicine or Physiology together with Niels Kaj Jerne in 1984 for "theories concerning the specificity in development and control of the immune system and discovery of the principle for production of monoclonal antibodies" (Ribatti, 2014). *In vivo* scientific research met with monoclonal antibodies with the discovery of hybridoma technology, and this breakthrough gave rise to some of the biggest scientific revolutions of the 21st century such as *in vivo* diagnostics, monoclonal antibody therapeutics and antibody-drug conjugates (ADCs) (Zaroff and Tan, 2019).

Hybridomas consist of a short-lived antibody generating B-cell fused with an immortal myeloma cell. This form of fused cells allows one specific monoclonal antibody type to be constitutively expressed in a large quantity. In addition to that, preferred hybridoma cell lines can also be cryopreserved to keep monoclonal antibody production long-lasting. For this reason, scientists most of the time prefer producing hybridomas on top of other monoclonal antibody production techniques with the intention of maintaining a convenient and continuous supply of crucial monoclonal antibodies (Zaroff and Tan, 2019).

2.7. The Progress of the Monoclonal Antibody Therapeutics Over Time

2.7.1. Mouse/Murine Sourced Monoclonal Antibodies

The first monoclonal antibody-based therapy was sourced by murine monoclonal antibodies, later by murine-human chimeras, followed by humanized and soon after human monoclonal antibodies. Each of these monoclonal antibody types have been accepted by Food and Drug Administration (FDA) as well as by other international agencies (Ribatti, 2014).

The first FDA approved monoclonal antibody drug for human use was Orthoclone OKT3 (muromonab), marketed by Ortho Biotech (J&J), a murine-sourced anti-CD3 monoclonal antibody, to be used in the treatment of organ transplant rejection (Ribatti, 2014). The drug was approved in 1986 when murine monoclonal antibodies were in clinical development.

2.7.2. Chimeric Monoclonal Antibodies

Even though the discovery of murine-sourced monoclonal antibodies are considered as a revolution for the pharmaceutical industry, they are frequently linked with allergic

responses, and the production of anti-drug antibodies that inhibit the therapeutic consequences of the drug. To deal with such adverse reactions, chimerization technology was developed by using genetic engineering tools as the complete antigen-specific domain of a mouse antibody was grafted on top of the constant domains of a human antibody (Ribatti, 2014).

Rituxan (rituximab), a mouse-human chimeric monoclonal antibody developed by Roche and approved by FDA in 1997, was the first monoclonal antibody to be used in the treatment of malignancy. It works against CD20 receptor expressed on the surface of B cells and promotes cell death in conditions such as lymphoma. Even though rituximab was initially developed for the treatment of lymphoma, it is progressively used for autoimmune diseases (Randall, 2016).

2.7.3. Humanized Monoclonal Antibodies

Zinbryta (daclizumab) by Biogen and AbbVie was the first humanized monoclonal antibody to be used against multiple sclerosis, approved by FDA in 1997. Followed by, Zenapax (daclizumab) by Roche was developed as a biosimilar to be used for organ transplant rejection (Reichert *et al.*, 2005). However, both of the drugs were withdrawn with the request of market authorization holders in 2009 and 2018 (EMA, 2009; FDA, 2018). Roche stated that discontinuation request was not due to any safety issue but to the decreasing market demand and the availability of alternative treatments in 2009. Contrary to that, Biogen and AbbVie had concerns about the risk/benefit balance of the drug after reports of meningoencephalitis in daclizumab use and 3 out of 12 cases were fatal (Williams and Chataway, 2019). Meningoencephalitis is a neurological disorder that brain and its adjacent protective membranes are inflamed because of viruses, bacteria, fungi, or other pathogens (Olsen *et al.*, 2015).

The discovery of daclizumab showed that humanization of monoclonal antibodies was possible, yet its toxicity was an indication that humanization technology was not the ultimate solution to ensure the safety of monoclonal antibody therapeutics.

2.7.4. Antibody-Drug Conjugates (ADCs)

When monoclonal antibody therapeutics are used in combination with other molecules such as protein toxins, immunomodulators, radionuclides, etc. in order to increase

or decrease the cytotoxicity depending on the disease mechanism, they are called antibody-drug conjugates (ADCs) (Zhao *et al.*, 2020).

The first FDA approved ADC was Mylotarg (gemtuzumab ozogamicin), an example of a monoclonal antibody combined with an immunotoxin, by Pfizer in 2000 to be used against acute myeloid leukemia (AML) disease. It was voluntarily discontinued in the United States after being marketed for 10 years. However, due to the vital unmet need of AML treatment it was introduced in the market again in 2018 with altered dosage and administration (Ribatti, 2014; Almagro *et al.*, 2018).

2.7.5. Fully Human Sourced Monoclonal Antibodies

Monoclonal antibodies have been continued to be the focus for scientists and developed with even more human-like constant domains (Almagro *et al.*, 2018). Along with improved techniques, Humira (adalimumab) by Abbott was the first fully human monoclonal antibody approved by FDA in 2002. The name stands for "**hu**man **m**onoclonal antibody **i**n **r**heumatoid **a**rthritis" (Lu *et al.*, 2020). The drug was obtained with phage display technology and turn out to be the most successful monoclonal antibody on the market, considering the effectiveness of the product. Currently, it is used for a broad range of autoimmune diseases such as psoriasis, rheumatoid arthritis, uveitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, juvenile arthritis, psoriatic arthritis, Behçet's syndrome and axial spondyloarthritis (Reimold, 2012; Kaplon and Reichert, 2019).

The Figure 2.6. shows the progress that have been made to increase safety of monoclonal antibodies by generating more human-like monoclonal antibodies.

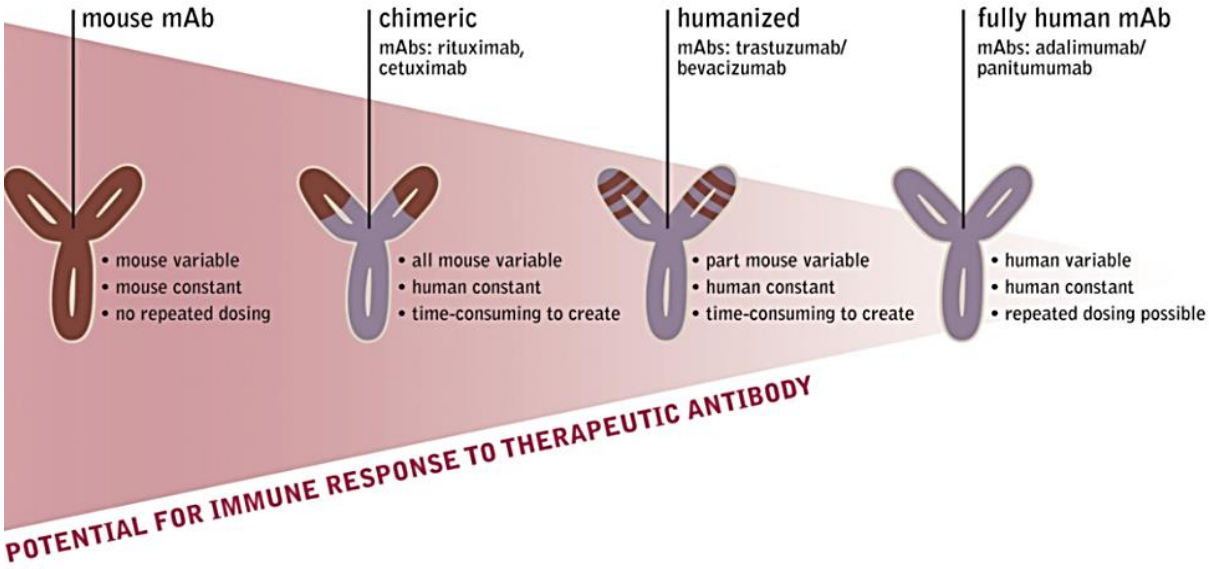

Fig. 2.6. The evolution of monoclonal antibodies from mouse-derived to fully human-sourced (Catapano and Papadopoulos, 2013).

Soon after, transgenic mice technology was developed for the production of fully human immunoglobulins. To achieve this, their own genes responsible for producing murine antibodies were inactivated and replaced with human antibody producing genes, followed by the traditional hybridoma technology to fuse antibody-producing mice cells with immortal cells to achieve continuous production. Transgenic technology result to better pharmacodynamic and pharmacokinetic aspects of monoclonal antibody therapeutics. Vectibix (panitumumab) by Amgen was the first completely human monoclonal antibody drug produced by using transgenic mice technology against colorectal cancer, FDA approved in 2006 (Ribatti, 2014; Almagro *et al.*, 2018; Lu *et al.*, 2020). The transgenic mice technology developed by Amgen is explained in Figure 2.7.

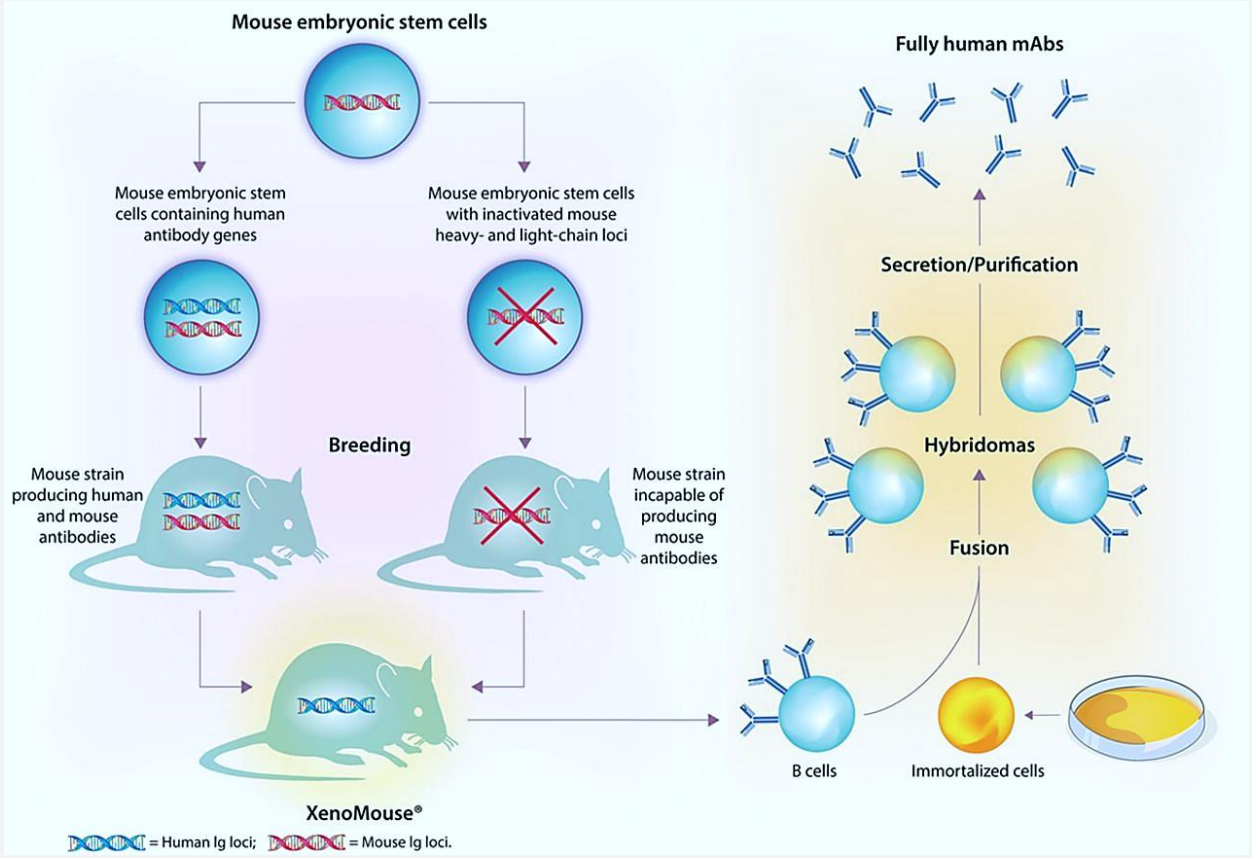

Fig. 2.7. The steps of fully human monoclonal antibody production by using transgenic mice and hybridoma technology developed by Amgen (Foltz et al., 2013).

2.7.6. Bispecific Monoclonal Antibodies

The advancements in the recombinant technology allowed monoclonal antibodies to evolve into bispecific antibodies. They provide two target specificities in a single antibody as they have two different binding domains within the same form, thus, increase the effectiveness compared to the combination of two single antibodies (Ribatti, 2014; Almagro *et al.*, 2018).

Three bispecific monoclonal antibodies, Removab (catumaxomab) by Neovii Biotech in 2009 in Europe only, Blincyto (blinatumomab) by Amgen in 2014, and Hemlibra (emicizumab) by Roche in 2017 were approved for medical use (Almagro *et al.*, 2018;

Sedykh *et al.*, 2018; Lu *et al.*, 2020). However, Removab was requested to be withdrawn by the market holder due to commercial reasons in 2017 (Lu *et al.*, 2020).

Removab and Blincyto both interact with cluster of differentiation 3 (CD3) on T-cells with one chain of the molecule, while other chain targets cancer cells generating epithelial cell adhesion molecule (EpCAM) or cluster of differentiation 19 (CD19), individually. Simultaneous interaction of bispecific antibodies with CD3 and EpCAM or CD19 makes cancer cells and T cells come closer resulting with very effective inactivation of the cancer cells (Almagro *et al.*, 2018).

Figure 2.8. shows catumaxomab interacting with EpCAM and CD3 as an example of how bispecifics work simultaneously.

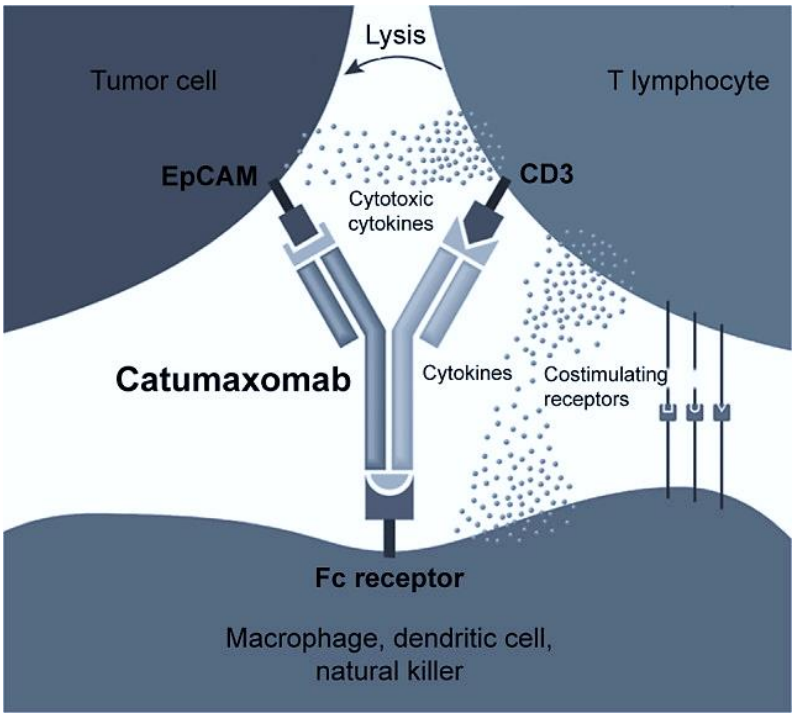

Fig. 2.8. Catumaxomab molecule interacting with EpCAM and CD3 (Sedykh et al., 2018).

Humanization of monoclonal antibodies, ADCs, phage-displayed libraries, the development of transgenic animals, as well as bispecific antibodies were among the emerged antibody technologies during the last 30 years (Almagro *et al.*, 2018).

The growth of the market value of monoclonal antibody drugs between the years 1975-2019 is given in Figure 2.9.

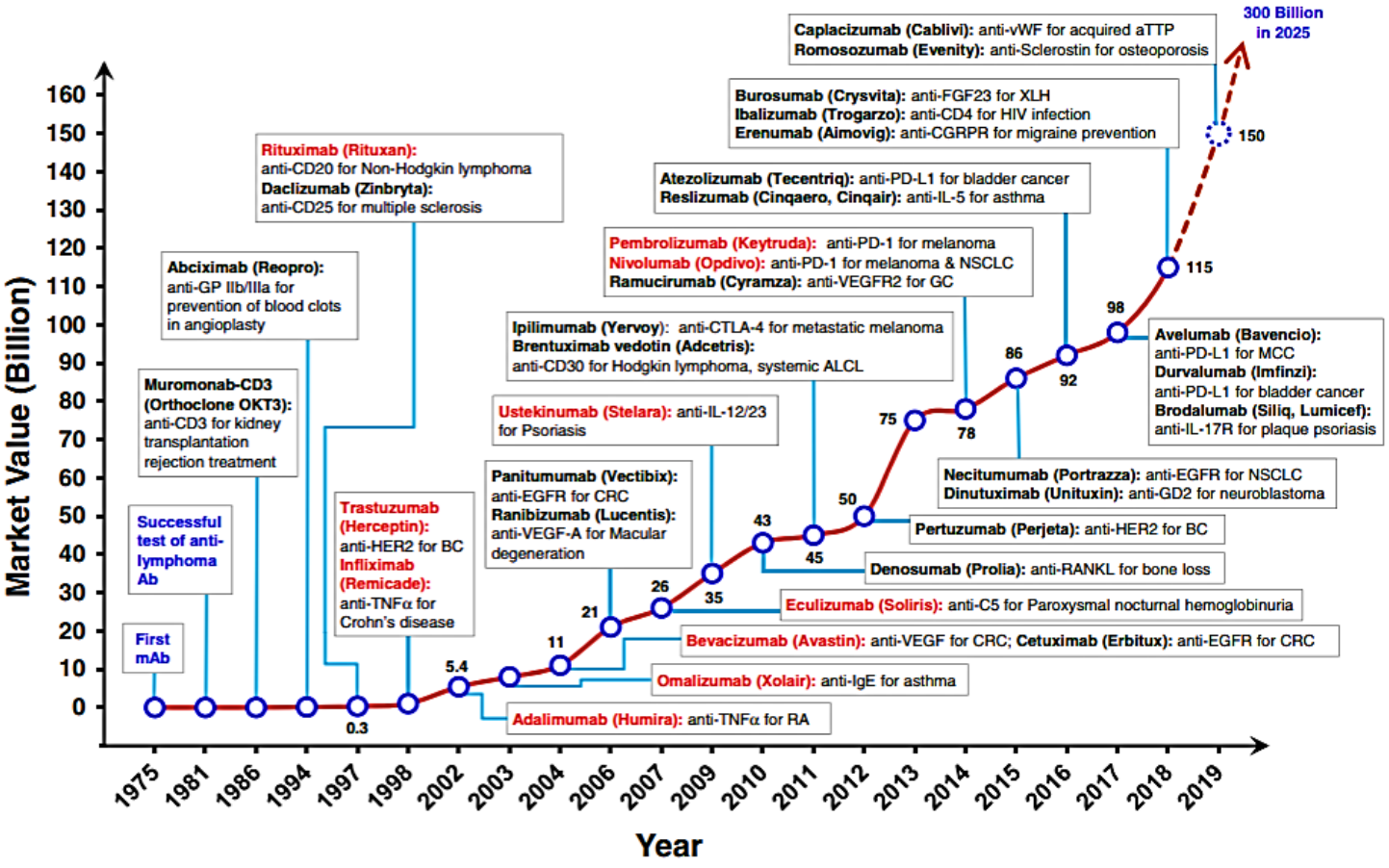

Fig. 2.9. The growth of the market value of monoclonal antibody drugs between 1975-2019 (Lu et al., 2020).

The full list of monoclonal antibody drugs that approved by major agencies and their sources of antigen-specific variable domains can be found in Appendix A and Appendix B (Strohl, 2014; Lu *et al.*, 2020).

2.7. Challenges in the Development and Therapeutic Use of Monoclonal Antibodies

2.7.1. Challenges in Drug Design

Use of animals is the most prominent challenge in the development of monoclonal antibodies. Understanding of immune response to biological medicinal products is a complicated process that depends on different variables which have not been completely clarified yet. Some of these factors can be uncertainties about the product, disease mechanism, animal species, or factors that are particular to patients (TreDenick, 2018).

To give an example, in the pre-clinical safety and toxicology tests, non-human primates (NHPs) are frequently used as they are one of the few species that monoclonal

antibodies show high pharmacological performance. Nevertheless, primate and human physiology can have vital differences resulting in concerns about safety and efficacy of the drug. The ongoing studies in bioinformatics aim to improve human safety predictions by using several algorithms to compare gene sequences of different species (Sewell et al., 2017; TreDenick, 2018). This approach will eventually minimize the animal use and reduce the challenge of translation between species in near future.

2.7.2. Challenges in Manufacturing

Monoclonal antibody therapeutics are excellent molecules by means of highly specific targeting, and show promise for the treatments of widespread diseases with no cure. However, they are complex molecules which can also have undesired biophysical assets that negatively impact on their manufacturing process (TreDenick, 2018). Some of these concerns can be:

- Insufficient expression,
- Instability,
- Random cross-reactivity,
- Weak pharmacokinetic activities

Monoclonal antibodies can either be administered as intravenous or subcutaneous. The average needed amount of monoclonal antibodies are ranging between a few hundred milligrams and 1 gram per dose to attain the desired concentration. According to FDA, the dose of a subcutaneous injection must not exceed 1,5 millilitre (mL). Thus, monoclonal antibody therapeutics are generally formulated denser than 100 mg/mL, which are extremely high levels of concentration that often lead to complexities in the production. Due to lack of space, highly dense environments in which monoclonal antibodies exist may cause to generation of reversible protein aggregates that increases the viscosity, and brings challenges at the filling stage (TreDenick, 2018; Razzaqi *et al.*, 2019).

On the other hand, sustaining the required product stability within a highly concentrated product is another challenge in manufacturing. Process or product-related impurities lead to instable molecules which carry high risk of degradation during or after manufacturing, when the product is being stored or shipped, and put the safety of the drug in a considerable threat (Schneider, 2008; TreDenick, 2018).

2.7.3. High Costs as a Consequence and Challenge to Patient Access

Eventually, all of the difficulties in the research, development, and manufacturing stages are eventually reflected in the expenses, which therefore affects the price of the product. Supporting that, monoclonal antibody therapeutics are considered amongst the most expensive drugs. To produce these biologics, mammalian cells are needed in vast number of cultures, as well as massive purification steps under Good Manufacturing Practice (GMP) circumstances are required, which results in exceptionally high manufacturing costs ($300/gram). To give an example, the cost of FDA-approved Raxibacumab, recombinant human antibody developed by Human Genome Sciences (HGS), was $5,100 per each dose when stockpiled (Gang Hu and Nagata, 2016). Likewise, the yearly supply of alemtuzumab to be used in the treatment of leukaemia costed approximately $61,000 in 2014 (Liu, 2014). As a consequence, the accessibility of monoclonal antibody therapeutics to every patient in need is another concern.

2.7.4. Side Effects and Safety Concerns

Even though monoclonal antibodies have been exposed to great interest by the pharmaceutical industry by means of their therapeutic applications and future potential, the adverse reactions are still present and unavoidable with the current technology (Santos *et al.*, 2018). The adverse reactions become much crucial if the monoclonal antibody type is not similar to human immune system (Santos *et al.*, 2018).

2.8. The Potential of Monoclonal Antibodies for the treatment of COVID-19 Pandemic

COVID-19, caused by an infection with severe acute respiratory syndrome coronavirus 2 (SARS-Cov2), occurred in Wuhan, China in December 2019 and was declared as “pandemic” by The World Health Organization (WHO) in March 2020 (WHO, 2020). It hit over 24 million people worldwide resulting in over 833,000 death by August 27, 2020.

There are multiple ongoing studies about the disease worldwide in which monoclonal antibodies show hope for the treatment of the global pandemic. The USA, The UK, China, South Korea, Germany, France, Italy, Switzerland, Singapore, Belgium are some of the countries in which several studies are being conducted about monoclonal antibody therapeutics to be used in the treatment of COVID-19 (CAS, 2020).

Not surprisingly, many institutions and universities have taken an immediate action to develop vaccine against the virus. However, developments in monoclonal antibody therapeutics are also as important as vaccine discovery (Ledford, 2020). This is especially because of the advantage that monoclonal antibodies require much shorter time to be developed compared to vaccines, which is a fascinating benefit when the incredibly spreading virus is considered in such pandemic, and also for being hope to patients who have already been infected. Furthermore, monoclonal antibody therapeutics are already a designer versions of the antibodies that would be produced by the immune system against SARS-CoV-2 with the presence of the vaccine in the circulation, therefore, they promise even a shorter distribution within the circulation as another advantage (Ledford, 2020).

According to Luo, (Luo *et al.*, 2020), exceedingly proinflammatory cytokines have been detected in high concentration in patients who died because of COVID-19. In addition to that, cytokine storms which trigger multiple organ dysfunction, cardiovascular failure, and immediate death, have been spotted in a great population of patients in critical condition due to overproduction of proinflammatory cytokines. Thus, treatment of cytokine storms together with their early detection and prevention play an important role for COVID-19 patients (Luo *et al.*, 2020).

Interleukin 6 (IL-6) is one of the cytokines involved in those cytokine storms stimulated by COVID-19. Therefore, tocilizumab, a humanized monoclonal antibody, is recommended as an anti-interleukin-6 receptor (anti IL-6R) for patients in critical conditions, prohibiting the accumulation of IL-6 (Luo *et al.*, 2020). Supporting this research, another study is being carried out in the University College Dublin (UCD) School of Medicine, and shows that patients with critical conditions avoid the need for mechanical ventilation with tocilizumab use, which is originally used in the treatment of inflammatory arthritis. 193 patients diagnosed with COVID-19 disease were assessed for the use of tocilizumab. 8 of them were deemed severe, and 6 of them were treated with tocilizumab at a maximum dose of 800 mg per injection with a repeated dose in every 12 hours. An immediate progress was observed in these six patients after the treatment, as they did not need ventilation support and discharged from the hospital in a week (McCarthy *et al.*, 2020; Gorey, 2020; Guaraldi *et al.*, 2020). According to the studies, treatment with tocilizumab is in correlation with a lowered

death or need of invasive mechanical ventilation. Tocilizumab is currently being tested in more than 55 clinical studies for COVID-19 patients (Kaplon *et al.*, 2020).

Another anti-rheumatoid "monoclonal antibody" drug levilimab, is being investigated as a possible treatment of COVID-19 that targets IL-6 receptor. By June 5, 2020 it obtained a state authorization in Russia only, through an accelerated procedure in accordance with the Decree No. 441 of the Government of the Russian Federation, effective as of April 4, 2020 as a result of a multicentre, randomized, double-blind and placebo-operated Phase III clinical trial (NCT04397562). This clinical trial was conducted with 204 participants who were administered a single dose mg 324 mg levilimab subcutaneously, combined with standard therapy and the results showed reduced lethality among the patients suffering with COVID-19 (Biocad, 2020; TAS, 2020). 10 out of 45 patients, including a 92-year-old-man, were discharged in the first 14 days of trials while the health condition of the remaining 35 patients endured satisfactory (CGTN, 2020).

Itolizumab, a humanized monoclonal antibody, is another urgently authorized medicine developed by Biocon and formerly approved in India for the treatment of plaque psoriasis. Emapalumab, canakinumab, ravulizumab are among other monoclonal antibody therapeutics that have already been marketed and currently under investigation for COVID-19 (Kaplon *et al.*, 2020).

2.9. Conceptual Framework

In accordance with the findings from the literature review, the promising aspects of the monoclonal antibodies are summarized as a conceptual framework in Figure 2.10.

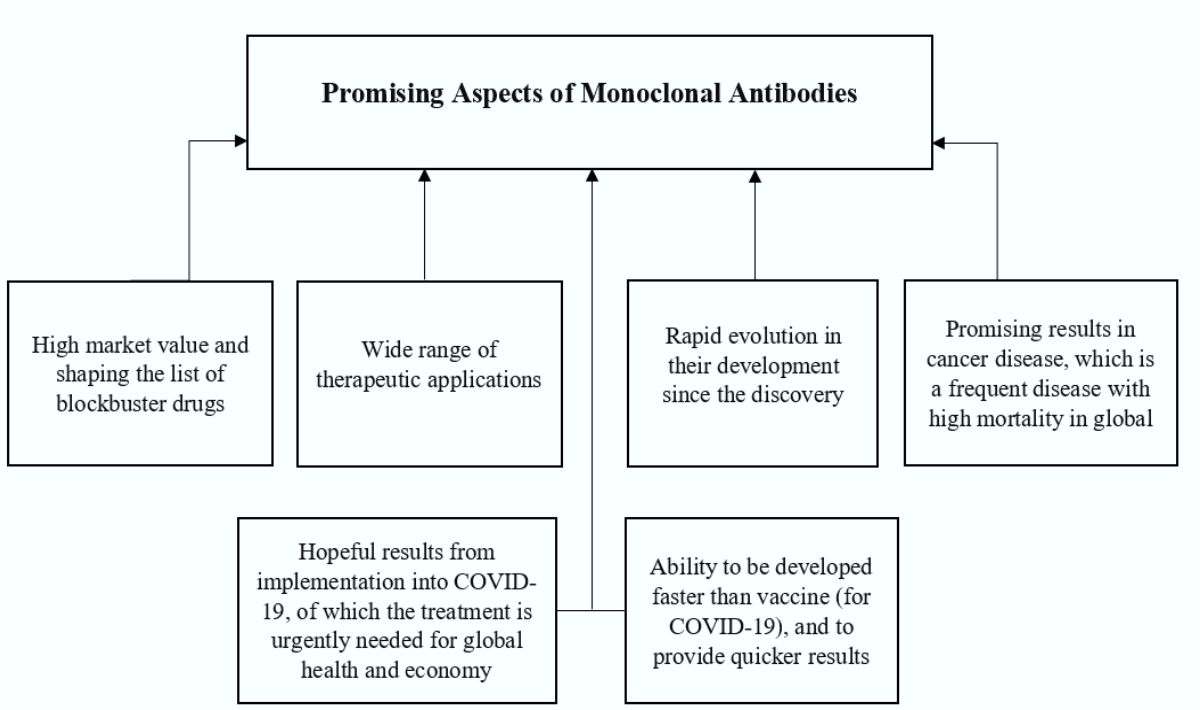

Fig. 2.10. The conceptual framework of the promising aspects of the monoclonal antibodies.

According to the findings from the literature review, the challenges in the development and therapeutic use of monoclonal antibodies are summarized as a conceptual framework in Figure 2.11.

Both of the conceptual frameworks will shape the research strategy is this study and form the pillars of the primary research. The research strategy is discussed in detail in the following section of the dissertation, Chapter III.

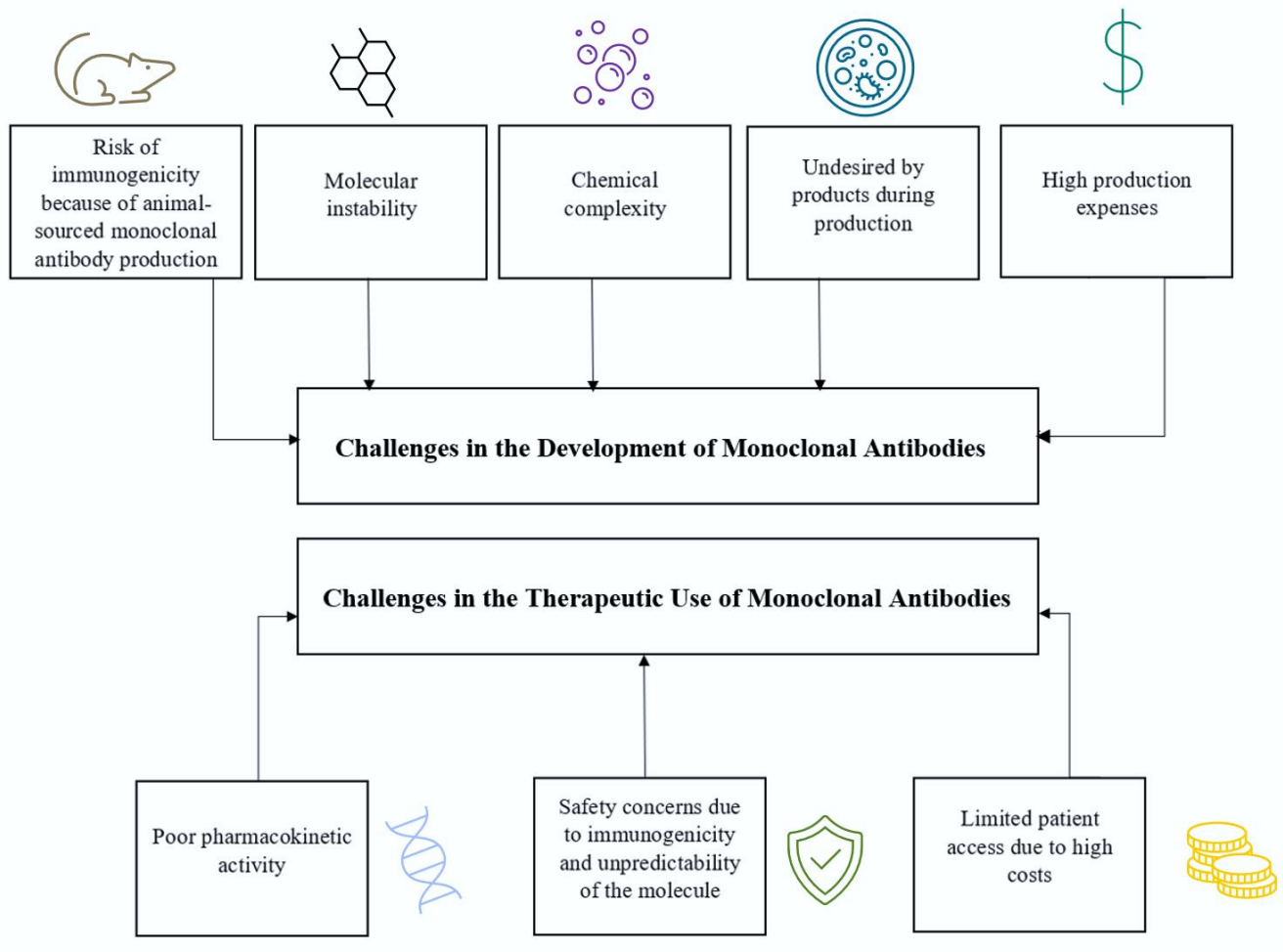

Fig. 2.11. The conceptual framework of the challenges in the development and therapeutic use of monoclonal antibodies.

CHAPTER III: RESEARCH METHODOLOGY AND METHODS

3.1. Research Philosophy

Research philosophy is a term used to describe the form of beliefs and assumptions in the knowledge improvement process of research, where assumptions are an integral part of the research as they form all aspects of projects and reflect the point of view of the researcher. There are three fundamental research philosophies (Saunders *et al.*, 2019):

- Ontological assumptions are about the nature of the truth, which influence what research objects and phenomena to concentrate on, how to see and approach them.
- Epistemological assumptions are based on the source of knowledge.
- Axiological assumptions consider the part of values and ethics throughout the research development, which integrate questions about how researchers manage their own values along with those of research participants.

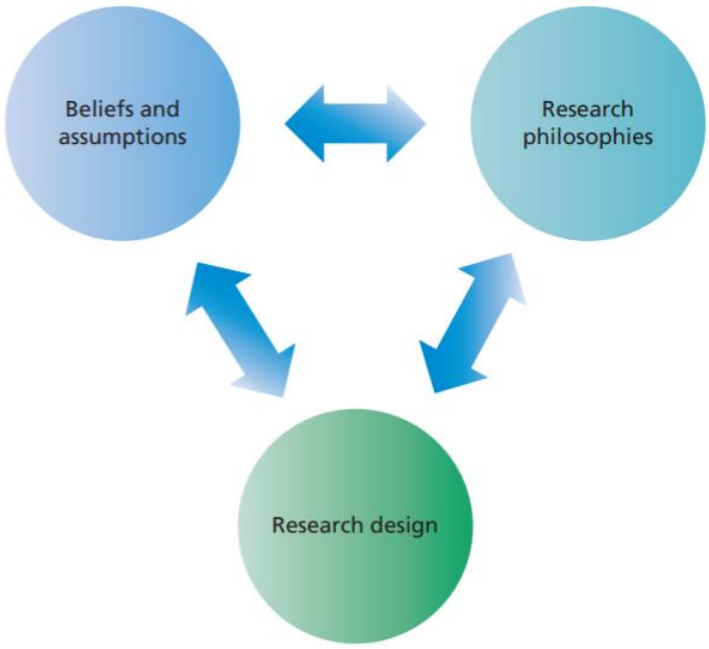

Fig. 3.1. The connection between beliefs and assumptions, research philosophies, and research design (Saunders et al., 2019).

Research philosophies also can be distinguished according to where their assumptions are assessed on the objectivism-subjectivism bands (Saunders *et al.*, 2019):

- Objectivism contains assumptions of the natural sciences. It implies realist ontology, epistemology centred on the finding of truth through observable and measurable facts, and represents a value-free, independent axiology.
- Subjectivism integrates assumptions of the arts and humanities. It implies nominalist ontology (which believes that social phenomena are shaped with the language, insights and resulting activities of social actors), epistemology centred on the thoughts, narratives, understandings, perceptions of social actors and represents a value-bound, reflexive axiology.

The variations and similarities in the ontological, epistemological, and axiological assumptions can root for various other paradigms to occur. Some of them are positivism, critical realism, interpretivism, relativism, pragmatism, determinism, etc. (Saunders *et al.*, 2019).

As part of this study titled *"Monoclonal Antibodies as Promising Therapeutic Agents in the Pharmaceutical Industry"*, the philosophy of **positivism** is more likely to be used in order to evaluate the progression of monoclonal antibody therapeutics over time since the discovery. The information to be used will be objective and based on scientific facts, thus, positivism was deemed more appropriate as this philosophy firmly centres on scientific empiricist methods intended to generate genuine information and facts regardless of the human influence (Saunders *et al.*, 2019).

However, there may not always be one truth about the identification of the challenges in the development and regulatory approval procedures of monoclonal antibodies. The challenges can be depending on the process, circumstances, different perceptions, or else. For this reason, and because of the fact that the determination of the difficulties would be the first step of problem-solving process, this part of the research will be conducted with a blended philosophy of **relativism** and **pragmatism** influences.

Similar to that, there is no one true reality when it comes to assess the implementation of monoclonal antibodies into recently emerged diseases, as well as to evaluate the potential of monoclonal antibodies as novel therapeutic agents in the pharmaceutical industry. This is because the therapeutic use of monoclonal antibodies is a brand-new technology and the uncertainties are ongoing, which makes the subject open to criticism combined with scientific facts. To give an example, tocilizumab, a monoclonal antibody that is mentioned in the

Chapter II, have been commonly used for the treatment for inflammatory diseases. Nevertheless, the possible therapeutic approach of tocilizumab against COVID-19 is now currently being discussed and investigated with limited information, as the drug has never been used in the treatment of infectious diseases, which allows the researcher to consider the philosophy of **critical realism**.

Likewise, analysis of the therapeutic use and challenges of monoclonal antibodies from different perspectives require interpretative information from different professionals in the associated disciplines even though it roots to a scientific concern. Thus, the philosophies **relativism** and **critical realism** will be included for this part as well.

3.2. Research Approach

According to Saunders, three fundamental approaches to generate theories for research are listed as:

- Deduction, when theories and hypotheses are generated prior to the research, and research strategy is intended to assess the hypotheses.
- Induction, when the information is gathered, and theories are developed as a consequence of the data evaluation.
- Abduction (also referred as "retroduction", especially by critical realists), when information is used to discover a fact, identify topics, and clarify relationships, in order to create a new theory or revise a current one which is consequently tested, frequently via extra data collection (Saunders *et al.*, 2019).

During this research, **abduction** approach will be taken into consideration for most of the time as there are many issues to uncover about the therapeutic use, production, challenges, and potential of monoclonal antibodies.

On the other hand, **induction** approach is deemed more appropriate for the primary research which concerns the assessment of therapeutic use and challenges of monoclonal antibodies from different perspectives of professionals in the associated disciplines, as this part of research will have a conclusion on its own that allows the researcher to build theories. Overall, the research approach to this study will consist of a blended form of **induction** and **abduction** approaches.

3.3. Methodological Choice

The representation of methodological choices and research design types is provided in Figure 3.2.

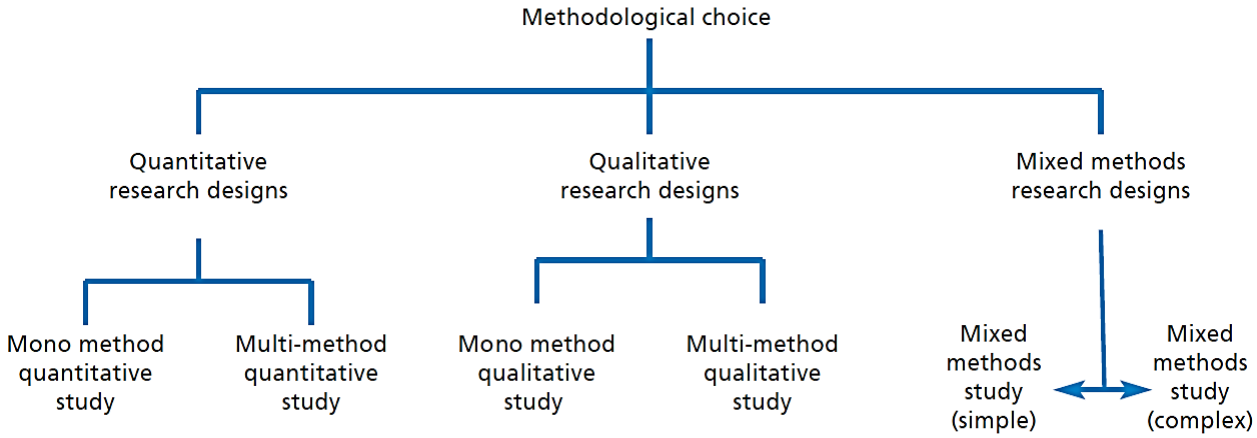

Fig. 3.2. Methodological choices and research design types (Saunders et al., 2019).

Methodological choice of a research relies on whether the data to be collected will be quantitative, qualitative or a mixed of both. The methodological choice is followed by determining on the method: mono, multi, or mixed methods as part of a research design.

- Quantitative research design is when the data collection relies on numbers, and results are generally presented as statistics, graphs, etc.
- Qualitative research design is independent from numeric data, which utilizes more of images, expressions, video clips, audio recordings, or other sources as material.
- Mixed research design consists of both quantitative and qualitative data. An example to this can be a questionnaire with both closed and open-ended questions (Saunders *et al.*, 2019).

In this research, both of quantitative and qualitative data will be generated, therefore, the research design will be **mixed**. Supporting that, according to Saunders, pragmatism and critical realism, which are the research philosophies of this study, are often associated with mixed method designs. The combination of quantitative and qualitative data can be either simple or complex:

- Mixed methods study (simple) is used when quantitative and qualitative data are collected separately.

- Mixed methods study (complex) is used when quantitative and qualitative data are collected sequentially.

As per the assessment of the progression of monoclonal antibody generation since the discovery, the current challenges in the development and therapeutic use of monoclonal antibody therapeutics, and their potential as novel therapeutic agents in the pharmaceutical industry, **qualitative** data will be used.

In order to analyse the different perspectives about therapeutic use and challenges of monoclonal antibodies by professionals from the associated disciplines, **quantitative** data will be collected. As the intention is to collect data from different perspectives, the number of participants is a concern. Quantitative data at this stage may help researcher to find more professionals to contribute the research, as the question types used for quantitative data are less time-consuming to answer. Therefore, larger number of professionals may volunteer to contribute, resulting in increased data accuracy.

3.4. Research Focus

The focus of a research can be exploratory, descriptive, explanatory, evaluative or a blend of these (Saunders *et al.*, 2019):

- Exploratory research aims to gain understanding about a topic of interest and tries to comprehend what is going on.
- Descriptive research intends to gain an exact profile of actions, individuals or conditions.
- Explanatory research creates casual connections among variables.
- Evaluative research aims to figure out how well something functions.
- Combination of different types on the other hand, may be achieved by following multiple techniques as per research design.

In this research, exploratory nature, combined with evaluative nature will be considered. Being one of the aspects of exploratory research, the route of this study may change according to new updates as COVID-19 pandemic is present and new insights may come up during the research. Exploratory research may also initiate with a wide focus which will eventually become narrower as the research develops (Saunders *et al.*, 2019). Almost all of the objectives of this research reflect evaluative nature, and root to understand how

efficient monoclonal antibodies work, how fast did the monoclonal antibody technology evolve, to what extent they show promise for diseases that are lack of treatment, and how did the market profile and investment focus of the pharmaceutical companies altered.

3.5. Research Strategy

There are different strategies in order to conduct a research project. Possible strategies can be listed as: experiment, survey, documentary and/or archival research, case study, ethnography, action research, grounded theory, narrative inquiry.

From the strategies above, this research will follow **survey** and **archival research** strategies. Many of the archival sources are currently available online, which allows researcher to find more information in a certain time and suitable to qualitative data collection. However, online sources are not always high of quality and reliable. To solve this problem, sources from academic websites will be considered to achieve the first and fourth research objectives:

- Science Direct
- National Centre for Biotechnology Information (NCBI)
- National Institute for Cellular Biology (NICB)
- National Institutes of Health (NIH)
- Social Science Research Network (SSRN)
- PubMed
- Google Scholar
- Griffith College Library – online sources, or organizational websites such as European Medicines Agency (EMA), Food and Drug Administration (FDA), and published academic books.

Survey on the other hand, is seemingly the most appropriate option in order to collect quantitative data for the remaining research objectives. Survey strategy may consist of questionnaire, structured observation and/or interviews as a data collection technique where questions are standardised and asked of all participants (Saunders *et al.*, 2019). To collect quantitative data from professionals regarding the therapeutic use and challenges about monoclonal antibodies, four questionnaires will be prepared to be presented to professionals in these fields:

- Scientists, who have a broad knowledge about the disease mechanism in which monoclonal antibodies are considered as possible drug candidates. They can evaluate the function of monoclonal antibody therapeutics specific to a disease.
- Medical Doctors, who can evaluate the use of monoclonal antibody therapeutics by means of health risks to patients. They can express more about the risk/benefit balance of monoclonal antibodies by giving real life examples from their patients.
- Regulatory Professionals, who can consider the monoclonal antibody use from a regulatory perspective.
- Pharmaceutical/Biotechnology Professionals, who can state their opinion about monoclonal antibody therapeutics from a more production and development – related perspective.

The consent form will be provided to all of the respondents before their participation to the questionnaire. A sample of the consent form can be found in Appendix C. Followed by, the first section (Section A) will also be common for each group of professionals to be asked name/surname, level of education, profession, area of specialty, and years of experience. Likewise, a sample of the Section A is provided in Appendix D. The respondents are presented in detail in Chapter IV, prior to analysis of the data.

The questionnaire will most of the time contain quantitative questions, and complex questions will be avoided to convince more professionals to contribute. The online questionnaire will be shared on LinkedIn platform also mentioned in two different webinars in order to find more participants:

- *"Therapy of Relapsed-Refractory Multiple Myeloma: Challenges and Current Options"*, by Springer Healthcare, held on June 24th, 2020.
- *"Understanding Genomics and Genetic Testing in Cancer Immunotherapy"*, by Cancer Research Institute, held on June 24th, 2020.

The Section B of the questionnaire will be specific for each group of professionals. However, some of the questions will remain same as long as the content is relevant. According to Chapter II, developing monoclonal antibody therapeutics are challenging overall. However, finding out the prominent factor which makes the process relatively more difficult than others, and focusing on its improvements would be the first step of the possible solutions. For this reason, as well as to achieve the second research objective, scientists and

pharmaceutical/biotechnology professionals will be asked six challenging factors in the development of monoclonal antibody therapeutics. The factors will include:

- Challenges in drug design and formulation,
- Challenges in chemical structure,
- Undesirable by products generated during manufacturing and processing,
- Uncertainties about the safety of monoclonal antibody therapeutics,
- Insufficient knowledge about the effectiveness of monoclonal antibody therapeutics,
- Challenges in biodistribution of the molecule.

All of the respondents will be asked if they agree that monoclonal antibodies are overpriced, after that if there is any governmental funding/support for the use and development of monoclonal antibodies in their country, aiming to gain an awareness about the global support for monoclonal antibodies.

Medical doctors, as the professionals who are the closest to patients, and therefore one of the most appropriate profession for the evaluation of the safety of the drugs, will be asked whether they agree monoclonal antibodies are safe to use for therapeutic approach. The effectiveness of monoclonal antibodies as a newly developed treatment for diseases, as well as the risk/benefit balance of monoclonal antibodies will be among the questions to be asked for scientists and medical doctors.

Additionally, regulatory professionals will be asked whether they agree that the regulations in their countries are adequate enough to ensure patient safety, product quality and efficacy. Moreover, they will be asked if they agree that regulatory differences between countries have a significant influence on the development/clinical use of monoclonal antibodies as a challenge, aiming to provide a brief overview to global regulatory perspective for monoclonal antibody therapeutics.

To achieve the third research objective, all of the respondents will be questioned about their agreement on future growth of therapeutic use of monoclonal antibodies. Moreover, there will be only one qualitative question for all respondents: "I would be very interested to hear from you if you would like to share any additional information, thoughts, or experience of working with monoclonal antibodies".

Quantitative results will be presented in tables and charts. Qualitative results will be provided as description in the tables. As a result, statistics will be both inferential and descriptive.

A sample of the Section B of the questionnaire for scientists can be found in Appendix E. Likewise, sample for medical doctors is provided in Appendix F, for regulatory professionals in Appendix G, and for pharmaceutical/biotechnology professionals in Appendix H.

3.6. Time Horizon

The time period of a research can be divided into two groups:

- Cross-sectional, when a research is completed at a certain time frame, and different population groups are observed.
- Longitudinal, when a research is conducted over a given period, sometimes taking many years, and same topics are observed over time (Saunders *et al.*, 2019).

This research will use cross-sectional time horizon, as there will be a time limitation and the topic will be assessed by different samples, such as assessment of regulatory, scientific, or medical perspective on monoclonal antibody therapeutics, or their development and challenges.

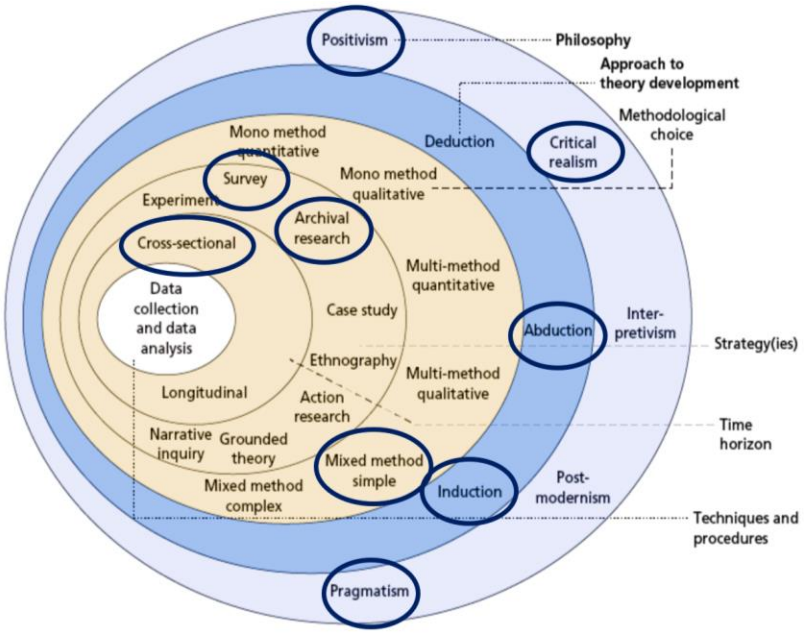

Fig. 3.3. Research onion (Saunders et al., 2019), and the followed techniques for this study.

3.7. Ethical Concern

Research ethics form a significant part of building the research design. This research will be conducted in accordance with the principles below:

- The researcher will avoid any activity that cause data inaccuracy such as fraud, dishonesty, deception, partiality, misrepresentation, etc. To give an example, all the questionnaires will be filled by real professionals in the required field, and their responses will not be altered. Likewise, the outcome of the research will not be falsified.
- The researcher will respect to the rights of the participants. Professionals will be informed that participation to the questionnaire is voluntary and they may withdraw at any time.
- The researcher will respect to the confidentiality of the participants. Their personal information will not be shared with public and the responses will be used for scholarly purposes only. As the questionnaire will be shared with public through LinkedIn, name/surname will be asked in order to prevent random participation of people with unmatched qualifications causing data inaccuracy. In case the researcher contacts directly with the possible participant, they will be offered a choice to participate anonymously as A.O. for instance, instead of Alara Ozen.
- Any activity that may cause embarrassment, pressure, discomfort, mental or physical harm, stress, pain or else to participants will be avoided (Saunders *et al.*, 2019).

CHAPTER IV: DATA ANALYSIS

This chapter will present the data and results obtained from the primary and secondary research, according to the research objectives.

4.1. Demographic Representations of the Respondents

4.1.1. The Various Professions of Respondents

The distribution of the participants according to their professions are shown in Table 4.1., and Figure 4.1.

Table 4.1. The representation of the number of the participants according to their professions.

Profession	Frequency	% Frequency
Scientists	45	45.91%
Medical Doctors	21	21.42%
Regulatory Professionals	7	7.14%
Pharmaceutical/biotechnology professionals	25	25.51%
Total	98	100%

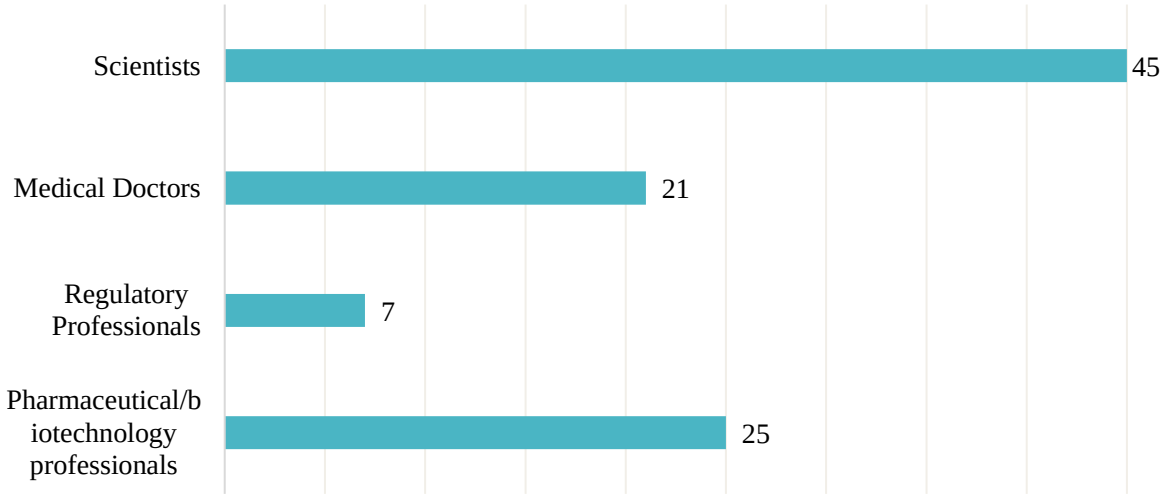

Fig. 4.1. The bar chart representing the number of the participants according to their professions.

The study was carried out with 45 scientists (45.91%), 21 medical doctors (21.42%), 7 regulatory professionals (7.14%), pharmaceutical/biotechnology professionals (25.51%), which accounts for 98 respondents in total.

4.1.2. The Highest Level of Education of the Respondents

The distribution of the participants according to their highest level of education are shown in Table 4.2., and Figure 4.2.

Table 4.2. The distribution of the highest level of education attained by the respondents according to their professions.

	BSc	**MSc**	**MD**	**PhD**	**Total**
Scientists	2 (2.04%)	20 (20.04%)	-	23 (23.46%)	45 (45.91%)
Medical Doctors	-	-	17 (17.34%)	4 (4.08%)	21 (21.42%)
Regulatory Professionals	1 (1.02%)	5 (5.10%)	-	1 (1.02%)	7 (7.14%)
Pharmaceutical/biotechnology Professionals	6 (6.12%)	11 (11.22%)	-	8 (8.16%)	25 (25.51%)
Total	9 (9.18%)	36 (36.73%)	17 (17.34%)	36 (36.73%)	98 (100%)

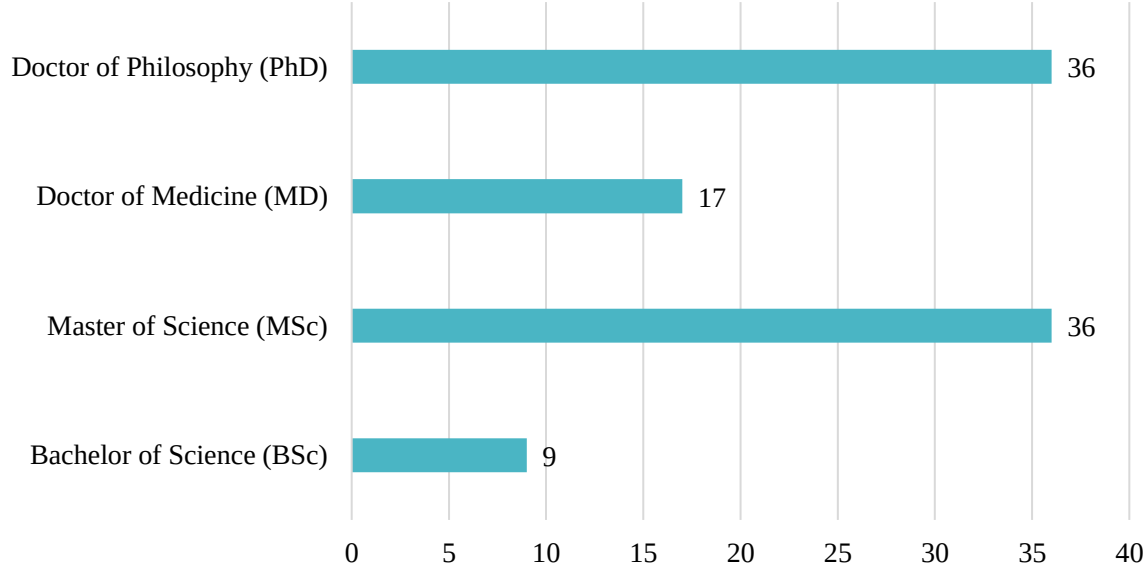

Fig. 4.2. The representation of the highest level of education attained by the respondents according to their professions.

Among the 98 respondents in total, 36 (36.73%) of them held PhD degree as the highest qualification, followed by 17 (17.34%) MD degree holders, 36 (36.73%) MSc degree attainders', and 9 (9.18%) participants with BSc degree.

The 36 respondents awarded with PhD degree consisted of 23 scientists, 4 medical doctors, a regulatory professional, and 8 pharmaceutical/biotechnology professionals. All of the 17 MD degree holders were medical doctors. Another group of 36 respondents with MSc holders included 20 scientists, 5 regulatory professionals, 11 pharmaceutical/biotechnology professionals. BSc holders with a number of 9 participants, comprised of 2 scientists, a regulatory professional and 6 pharmaceutical/biotechnology professionals.

4.1.3. The Experience with Monoclonal Antibody Therapeutics of the Respondents

The participants were asked if they have had any working experience with monoclonal antibody therapeutics, which could be in the research and development, regulatory procedure, or manufacturing department, as well as treating patients with monoclonal antibodies, depending on the profession of the respondents. The results are given in Table 4.3., and Figure 4.3.

Table 4.3. The respondents according to their experience of working with monoclonal antibodies.

	Yes	**No**
Scientists	31 (31.63%)	14 (14.28%)
Medical Doctors	11 (11.22%)	10 (1.02%)
Regulatory Professionals	7 (7.14%)	-
Pharmaceutical/biotechnology professionals	21 (21.42%)	4 (4.08%)
Total	70 (71.42%)	28 (28.57%)

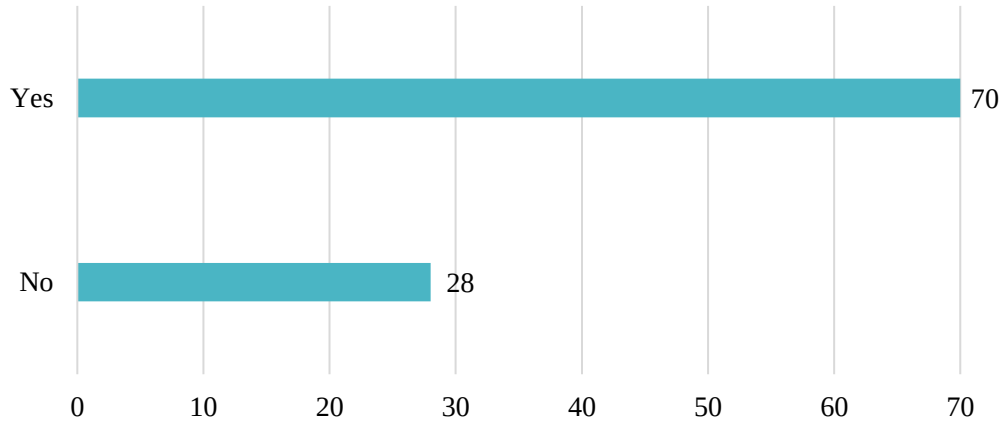

Fig. 4.3. The demonstration of the respondents according to their experience of working with monoclonal antibodies.

31 (31.63%) scientists, 11 (11.22%) medical doctors, 7 (7.14%) regulatory professionals, 21 (21.42%) pharmaceutical/biotechnology professionals, that accounts for 70 participants overall (71.4%), have stated that they have had working experience with monoclonal antibodies. On the other hand, 28 participants (28.57%) consisting of 11 scientists, 10 medical doctors, 4 professionals from the pharmaceutical/biotechnology industry have stated that they have not had any experience of working with monoclonal antibodies.

4.2. Analysis of the Objective 1: Assessment of the progression of monoclonal antibody generation over time to provide better quality, safety and efficiency of the product and advance its therapeutic use.

The pharmaceutical industry has made a great progress by means of their approach to develop monoclonal antibody types with reduced immunotoxicity. Development of human-like or human-sourced monoclonal antibodies plays a key role in this issue. In order to assess the progression that the pharmaceutical industry has made so far, the antibody formats of approved monoclonal antibody therapeutics within the 10 years is given in Table 4.4., and Figure 4.4, with a separate presentation of [2010-2014] and [2015-2019] for a better comparison. The sources of the list of approved drugs by years and their antibody formats can be found in Appendix A and Appendix B (Strohl, 2014; Lu *et al.*, 2020).

Table 4.4. The distribution of globally marketed monoclonal antibody therapeutics according to their antibody format.

Period	Mouse/Murine	Chimeric	Humanized	Human	Total
2010-2014	1 (1.25%)	2 (2.50%)	7 (8.75%)	6 (7.5%)	16 (20%)
2015-2019	1 (1.25%)	2 (2.50%)	23 (28.75%)	18 (22.50%)	64 (80%)
Total	2 (2.50%)	4 (5%)	30 (37.50%)	2 (30%)	80 (100%)

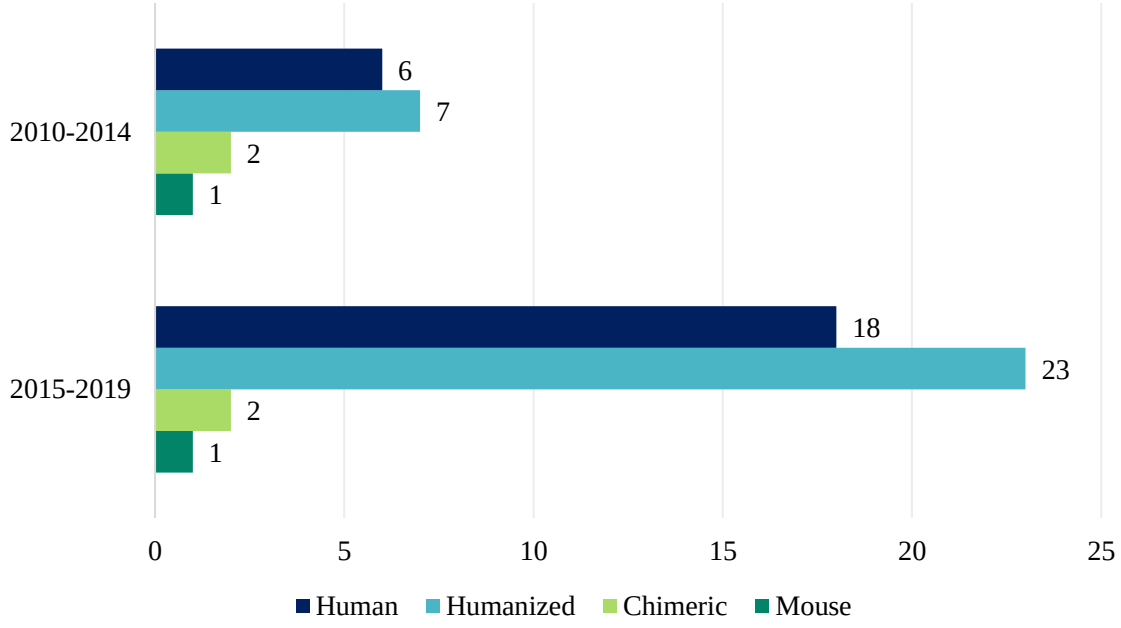

Fig 4.4. The representation of globally marketed monoclonal antibody therapeutics between 2010-2014 and 2015-2019 according to their antibody format (Strohl, 2014; Lu et al., 2020).

According to Table 4.4., and Figure 4.4., the number of approved monoclonal antibody therapeutics between [2010-2019] was 80. Throughout the 10-year period of time, only 16 (20%) therapeutics year was approved in the first half period, which included 1 mouse/murine, 2 chimeric, 7 humanized, 6 human sourced monoclonal antibodies. The second 5-year period comprises 64 (80%) therapeutics which included a mouse/murine, 2 chimeric, 23 humanized and 18 human sourced monoclonal antibodies.

4.3. Analysis of the Objective 2: Identification of the current challenges in the development and therapeutic use of monoclonal antibody therapeutics.

The current difficulties in the development of monoclonal antibody therapeutics have previously been mentioned within the Chapter II. In parallel to those findings, respondents were asked various questions about the challenges depending on their profession.

4.3.Q1: Do you agree that there are certain factors can influence the development process of monoclonal antibodies?

The scientists and professionals from the pharmaceutical/biotechnology industry were asked six possible factors that can impact on the development process of monoclonal antibodies as their profession were deemed the most relevant for this question. 45 scientists and 25 pharmaceutical/biotechnology industry professionals that accounts for 70 respondents in total were questioned. The results are shown in Table 4.4, also represented in Figure 4.4 as bar charts.

Table 4.5. The point of view of the scientists and pharmaceutical/biotechnology professionals for the factors that can influence the development of monoclonal antibodies.

Factors	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Total
Drug design and formulation	29 (41.42%)	28 (40%)	10 (14.28%)	3 (4.28%)	-	70 (100%)
Chemical structure	22 (31.42%)	27 (38.57%)	14 (20%)	5 (7.14%)	2 (2.85%)	70 (100%)
Undesirable by products generated during manufacture and processing	17 (24.28%)	33 (47.14%)	14 (20%)	6 (8.57%)	-	70 (100%)
Uncertainties about the safety of monoclonal antibody therapeutics	17 (24.28%)	30 (42.85%)	12 (17.14%)	8 (11.42%)	3 (4.28%)	70 (100%)
Insufficient knowledge about the effectiveness of monoclonal antibody therapeutics	11 (15.71%)	27 (38.57%)	14 (20%)	14 (20%)	4 (5.71%)	70 (100%)

Biodistribution of the molecule	21 (30%)	32 (45.71%)	13 (18.57%)	4 (5.71%)	-	70 (100%)

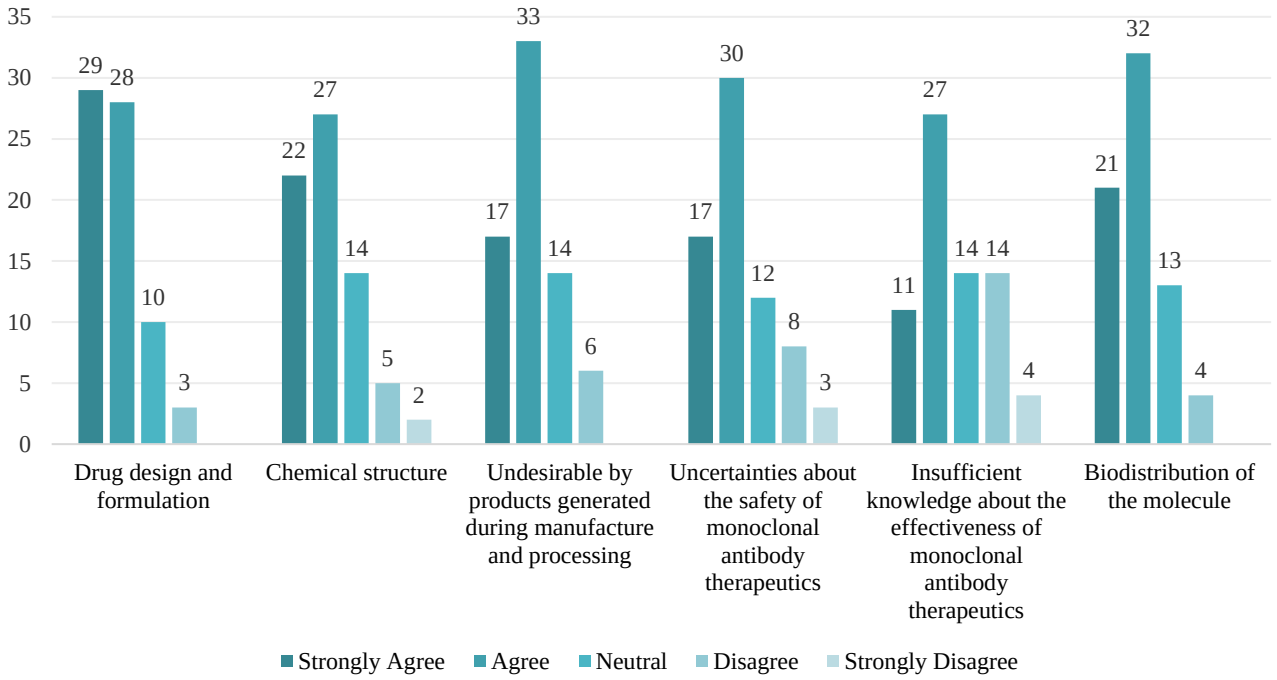

Fig. 4.5. The demonstration of the viewpoints of the scientists and pharmaceutical/biotechnology professionals for the factors that can influence the development of monoclonal antibodies.

Of the 70 respondents that consisted of scientists and pharmaceutical/biotechnology professionals, 57 (81.42%) agreed with the statement that drug design and formulation is a challenging factor that can influence the quality and the development of the monoclonal antibody therapeutics, of which 29 among them even strongly agreed. 10 respondents (14.28%) felt neutral with the statement, while 3 (4.28%) disagreed.

Chemical structure of monoclonal antibodies was given as another challenge that can influence the development of monoclonal antibodies. According to the results, 49 respondents (70%) believed that chemical structure is a factor that requires critical consideration in the development process, of which 22 among them even strongly believed. 14 (20%) felt neutral, while 7 (10%) disagreed.

A vast majority of the respondents, 50 (71.42%) agreed with the statement that undesirable by products generated during manufacture and processing can have a crucial impact on the quality, safety, and efficacy of the monoclonal antibody therapeutics of which

17 among the supporters of this statement even strongly agreed. 14 (20%) felt neutral. 6 (8.57%) participants on the other hand, disagreed.

47 (67.14%) of the 70 respondents agreed with the statement that the current knowledge about monoclonal antibody therapeutics is not adequate to ensure their safety, of which 17 among them even strongly agreed. 12 (17.14%) respondents remained neutral, while 11 (15.71%) disagreed.

Likewise, another group of 38 (54.28%) respondents were in favour of the statement that the existing information is not sufficient to state that monoclonal antibody therapeutics are effective. 14 (20%) professionals felt neutral. 27 (38.57%) of the respondents were in disagreement with the statement, of which 14 of them even strongly disagreed.

Biodistribution of monoclonal antibody therapeutics was given as the final factor in which large number of respondents, 53 (75.71%), considered it as a challenge for the development of monoclonal antibodies while 13 (18.57%) professionals felt neutral, 4 (5.71%) disagreed.

Overall, with a significant percentage of 81.42% among scientists and pharmaceutical/biopharmaceutical professionals, drug design and formulation is considered as the most challenging factor that impacts on the development of monoclonal antibodies, followed by biodistribution of the molecule (75.71%), undesirable by products generated during manufacture and processing (71.42%), and chemical structure (70%). Uncertainties about the safety of the product (67.14%) and insufficient knowledge about the effectiveness of monoclonal antibody therapeutics (54.28%) were considered less problematic compared to other factors but yet the percentage of the supporters of these factors is above average.

4.3.Q2. Do you agree or disagree with the statement that monoclonal antibodies are overpriced?

The high costs of monoclonal antibody therapeutics as a challenge to patients' access have previously been discussed in the Chapter II. Relating to that, all of the respondents were asked about the economic situation of monoclonal antibody therapeutics. The results are shown in Table 4.6., and Figure 4.6.

Table 4.6. The points of views of the total respondents to the question whether they find monoclonal antibodies overpriced.

Respondents	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
98 (100%)	19 (19.38%)	40 (40.81%)	27 (27.55%)	9 (9.18%)	3 (3.06%)

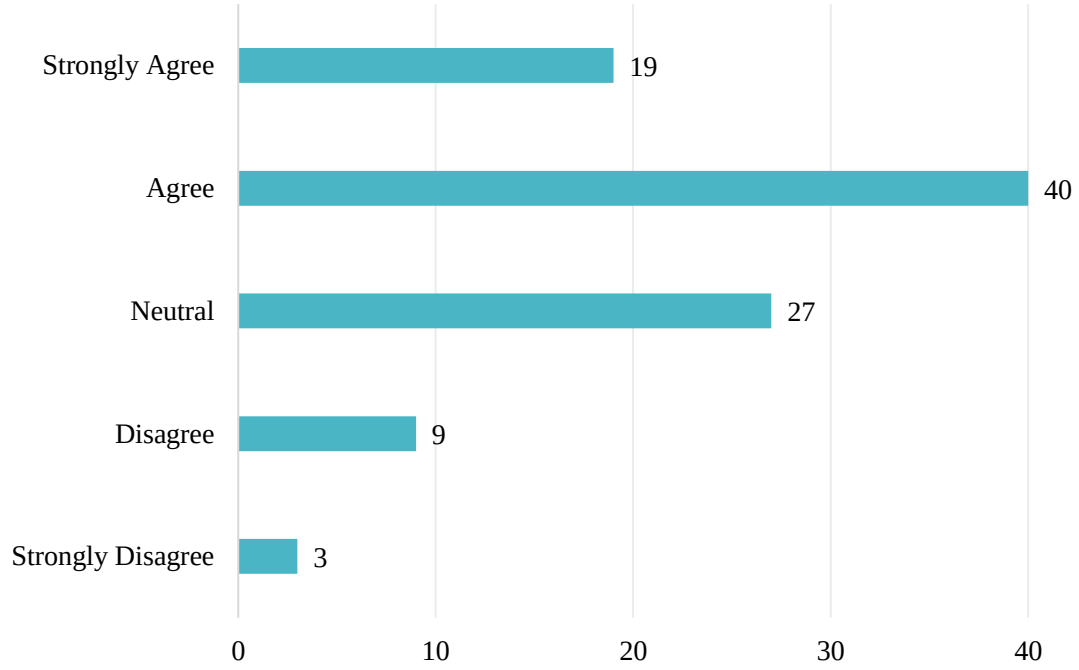

Fig. 4.6. The demonstration of the points of views of the total respondents to the question whether they find monoclonal antibodies overpriced.

59 (60.20%) of the 98 participants, representing the majority, agreed with the statement that monoclonal antibodies are overpriced. 27 of the respondents (27.55%) felt neutral, while 12 (12.24%) disagreed. Two respondents of the 27 who opted for neutral, stated that they believe monoclonal antibodies are equally expensive to produce.

4.3.Q3: Is there any governmental funding/support in your country for the use or development of biologics/monoclonal antibodies?

As a consequence of the various challenging factors in the generation of monoclonal antibodies; research and development process as well as manufacturing can consist of many repeated actions to attain a high quality, safe and effective product in the end. Likewise, the high expenses throughout the process which reflects to patients' access to these therapeutics

was identified as another difficulty. At this point, governmental funding/support can have a significant impact on the improvements for monoclonal antibody development. For this reason, respondents were asked if they have any governmental funding/support in their country for the use or development of monoclonal antibodies. The aim for asking this question was to gain awareness about the global support for monoclonal antibodies. The results obtained are shown in Table 4.7., and Figure 4.7.

Table 4.7. The outcomes from the respondents questioned whether any governmental funding/support exists in their country for the use or development of biologics/monoclonal antibodies.

Respondents	Yes	No	Other
98 (100%)	51 (52.04%)	31 (31.63%)	16 (16.32%)

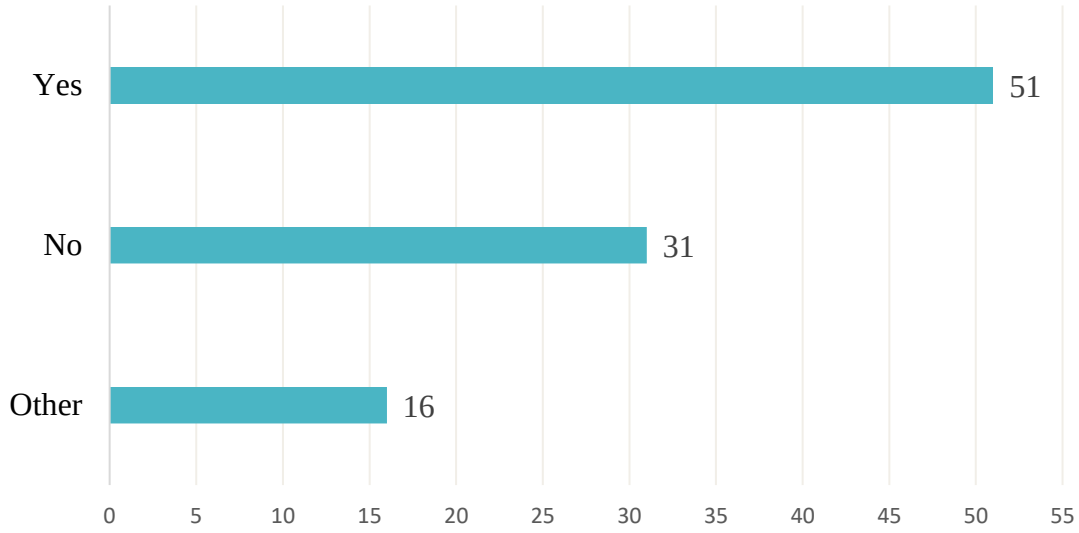

Fig. 4.7. The representation of the outcomes from the respondents questioned whether any governmental funding/support exists in their country for the use or development of biologics/monoclonal antibodies.

51 respondents out of 98 (52.04%) stated that they have governmental support for the use or development of biologics/monoclonal antibodies, while 31 (31.63%) answered negatively, and 16 (16.32%) were unsure if any support existed in their country.

32 of the respondents (32.65%) provided the type of the governmental support and the country. The specified answers are shown in Table 4.8.

Table 4.8. The countries and the type of the governmental funding/support for the use and development of monoclonal antibodies, according to the answers obtained from the questionnaire.

Country	Organization
The USA	• Food and Drug Administration (FDA), • National Institutes of Health (NIH), • Biomedical Advanced Research and Development Authority (BARDA), • *"Medicare and Medicaid exist in the USA, which governs the kind of treatment for particular age groups and categories of patients. It mainly covers prescription medicine, but since a few years back, we now have the addition of biologics to the list of treatments undertaken by these schemes"*
India	• Biotechnology Industry Research Assistance Council (BIRAC) • Central Drugs Standard Control Organisation (CDSCO) • Indian Council of Medical Research (ICMR) • The Department of Science and Technology (DST) • Department of Biotechnology (DBT)
Ireland	• Industrial Development Authority (IDA) • Science Foundation Ireland (SFI) • Enterprise Ireland • *"Depending on the indication, some types of monoclonal antibodies are reimbursed in Ireland."*
Turkey	• The Scientific and Technological Research Council of Turkey (TUBITAK) • Health Institutes of Turkey (TUSEB) • Turkish Social Security Agency (SGK)
Norway	• The Research Council of Norway • Innovation Norway • Life Science Cluster

Germany	• German Research Foundation (DFG)
The UK	• Cancer Research UK (CRUK)

Table 4.8 shows that 32.65% of the respondents were aware of the governmental support/funding in the specified countries.

4.3.Q4: Do you agree or disagree with the statement that monoclonal antibody therapeutics are safe to use?

In order to analyse the safety concern for the therapeutic use of monoclonal antibodies from real-life examples, the viewpoints of medical doctors were asked independently from other professionals. The results are presented in Table 4.9., and Figure 4.8.

Table 4.9. The perspective of medical doctors whether they agree that monoclonal antibodies are safe to use.

	Strongly Agree	**Agree**	**Neutral**	**Disagree**	**Strongly Disagree**	**Total**
Medical Doctors	4 (19.04%)	14 (66.66%)	3 (14.28%)	-	-	21 (100%)

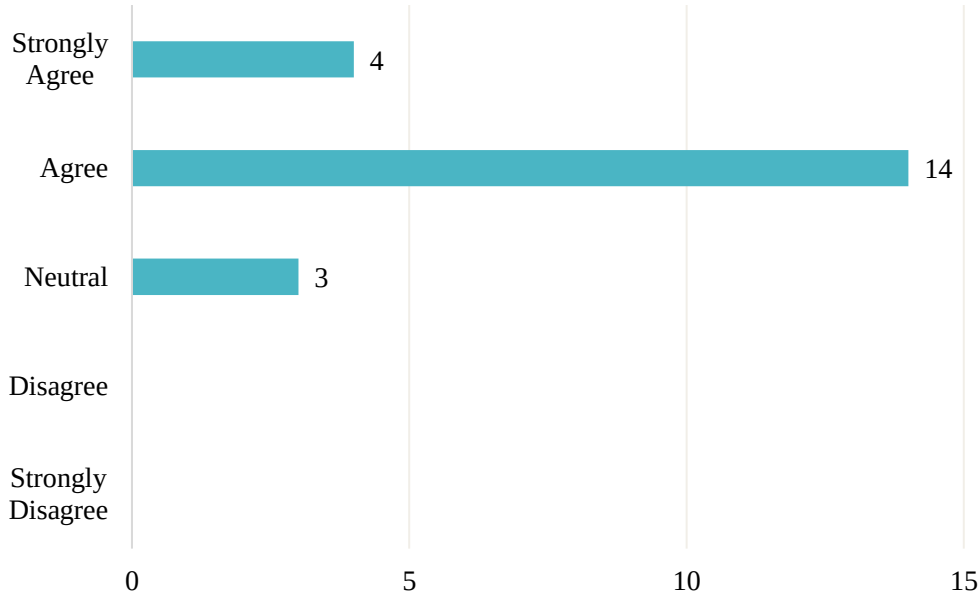

Fig. 4.8. The representation of the perspective of medical doctors whether they agree that monoclonal antibodies are safe to use.

A vast majority of medical doctors, 18 (85.71%) out of 21, were in favour with the statement that therapeutic use of monoclonal antibodies is safe. 3 (14.28%) doctors remained neutral, while none of them disagreed.

4.3.Q5: Do you agree or disagree with the statement that monoclonal antibodies are effective as a newly developed treatment for diseases?

The effectiveness of the monoclonal antibodies for the most frequent application area of them was asked to both scientists and medical doctors, as a scientist is more skilled in evaluating the disease-drug mechanism in a molecular scale, while a doctor can consider real life examples through their patients. This question was answered by 45 scientists and 21 medical doctors, which accounts for 66 people in total. The findings are shown in Table 4.10 and Figure 4.9.

Table 4.10. The perception of scientists and medical doctors whether they find monoclonal antibodies effective as a newly developed treatment for diseases.

Respondents	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Total
Scientists	9 (13.63%)	22 (33.33%)	14 (21.21%)	-	-	45 (68.18%)
Medical Doctors	8 (12.12%)	10 (15.15%)	2 (3.03%)	1 (1.51%)	-	21 (31.81%)
Total	17 (25.75%)	32 (48.48%)	16 (24.24%)	1 (1.51%)	-	66 (100%)

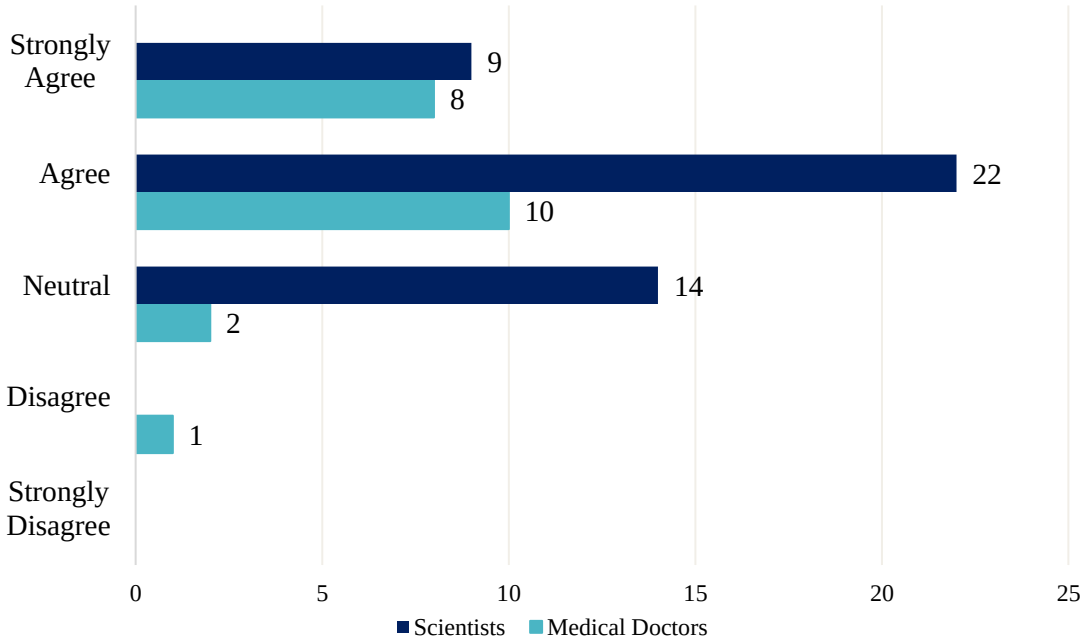

Fig. 4.9. The representation of the perception of scientists and medical doctors whether they find monoclonal antibodies effective as a newly developed treatment for diseases.

31 scientists and 18 medical doctors, which accounts for 49 (74.24%) of the 66 respondents supported the statement that monoclonal antibodies are effective as a newly developed treatment for diseases, while 16 (24.24%) remained neutral, and 1 (1.51%) disagreed.

When the statistics are evaluated individually according to the professions, 31 (68.88%) of the 45 scientists and 18 (85.71%) of the 21 medical doctors agreed. 14 (31.11%) out of 45 scientists and 2 (9.52%) out of 21 medical doctors felt neutral.

4.3.Q6: Do you agree or disagree with the statement that the benefits of monoclonal antibodies outweigh the risks?

A group of 66 respondents, which includes 45 scientists and 21 medical doctors were questioned if they agree with the statement that benefits of monoclonal antibodies outweigh the risks. The findings are shown in Table 4.11 and Figure 4.10.

Table 4.11. The responses of scientists and medical doctors whether they agree to the statement that benefits of monoclonal antibodies outweight the risks.

Respondents	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
66 (100%)	13 (19.69%)	32 (48.48%)	19 (28.78%)	2 (3.03%)	-

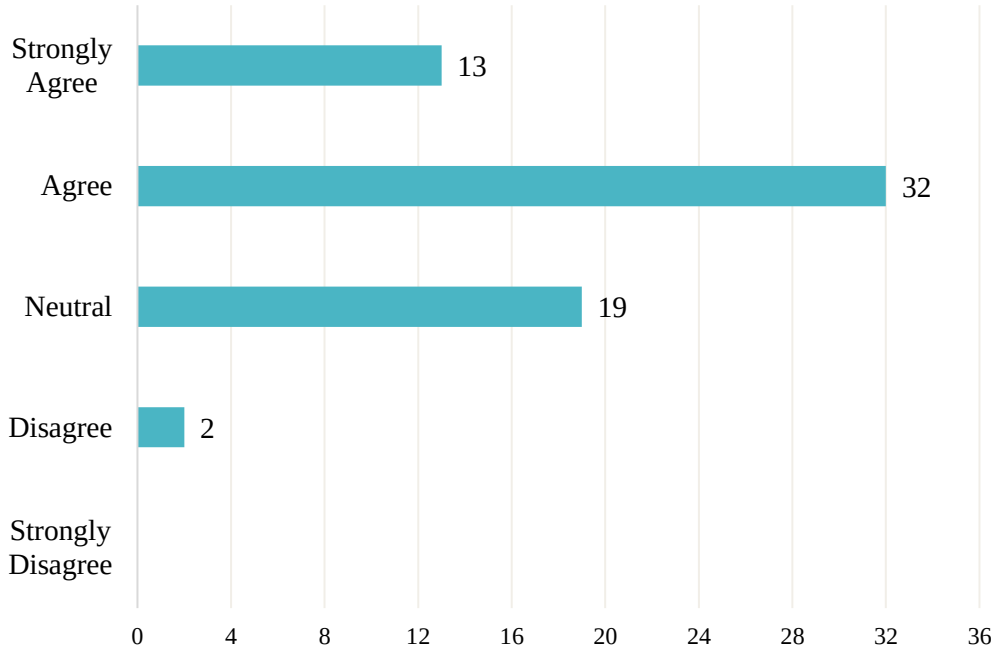

Fig. 4.10. The representation of the perception of scientists and medical doctors on the benefit/risk balance of monoclonal antibodies.

45 (68.18%) respondents out of 66 agreed with the statement that monoclonal antibodies are beneficial and worth to use even though they carry risks. 19 (28.78%) respondents felt neutral, 2 (3.03%) respondents disagreed.

The questions 4.3.Q7 and 4.3.Q8 were as part of the opportunity to ask regulatory professionals individually who work in consultancy companies for biotechnology industry, from countries including the USA, Ireland, India. The purpose was to provide a brief overview to global regulatory perspective for monoclonal antibody therapeutics.

4.3.Q7: Do you agree or disagree with the statement that the regulations for biologics/monoclonal antibodies in your country are adequate enough to ensure product efficacy, quality, and patient safety?

Table 4.12. The point of views of the regulatory professionals on their agreement or disagreement that the regulations for biologics/monoclonal antibodies in their country are adequate enough to ensure product efficacy, quality, and patient safety.

Respondents	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
7 (100%)	2 (28.57%)	3 (42.85%)	2 (28.57%)	-	-

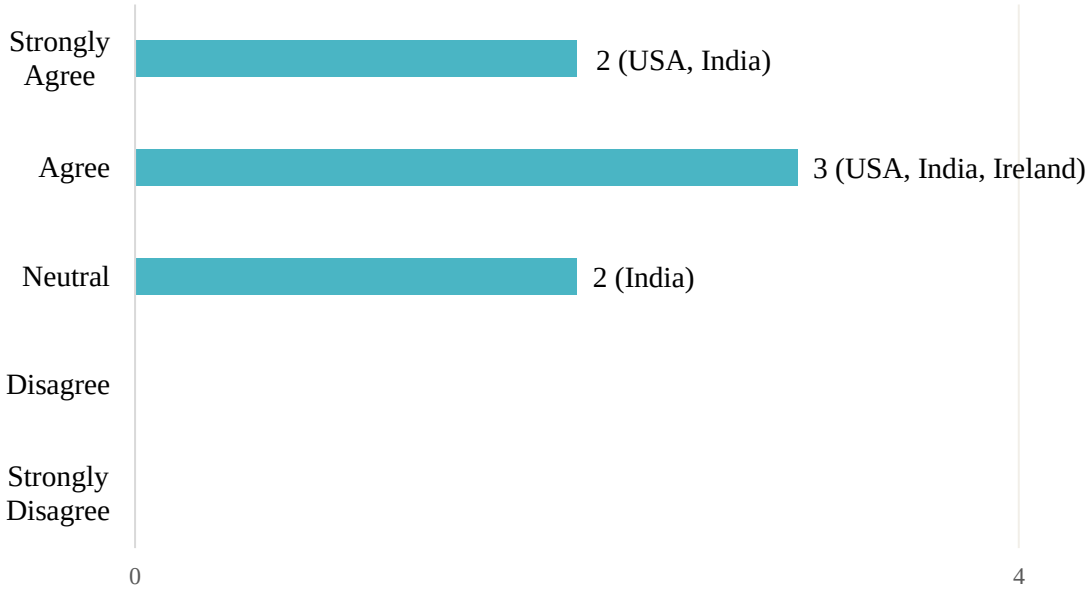

Fig. 4.11. The representation of the point of views of the regulatory professionals on their agreement or disagreement that the regulations for biologics/monoclonal antibodies in their country are adequate enough to ensure product efficacy, quality, and patient safety.

5 (71.42%) of the 7 regulatory professionals supported the statement that the regulations for biologics/monoclonal antibodies in the USA, India, and Ireland are adequate enough to ensure product efficacy, quality, and patient safety. 2 (28.57%) of the regulatory professionals from India remained neutral, while none of the respondents disagreed.

4.3.Q8: Do you agree or disagree with the statement that regulatory differences between countries have a significant impact on the development/clinical use of monoclonal antibodies?

Table 4.11 and Figure 4.12 presents the point of views of the regulatory professionals whether they agree to the statement that regulatory differences between countries have an important influence on the development/clinical use of monoclonal antibodies.

Table 4.13. The perceptions of the regulatory professionals on their agreement or disagreement that regulatory differences between countries have a significant impact on the development/clinical use of monoclonal antibodies.

Respondents	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
7 (100%)	4 (57.14%)	1 (14.28%)	2 (28.57%)	-	-

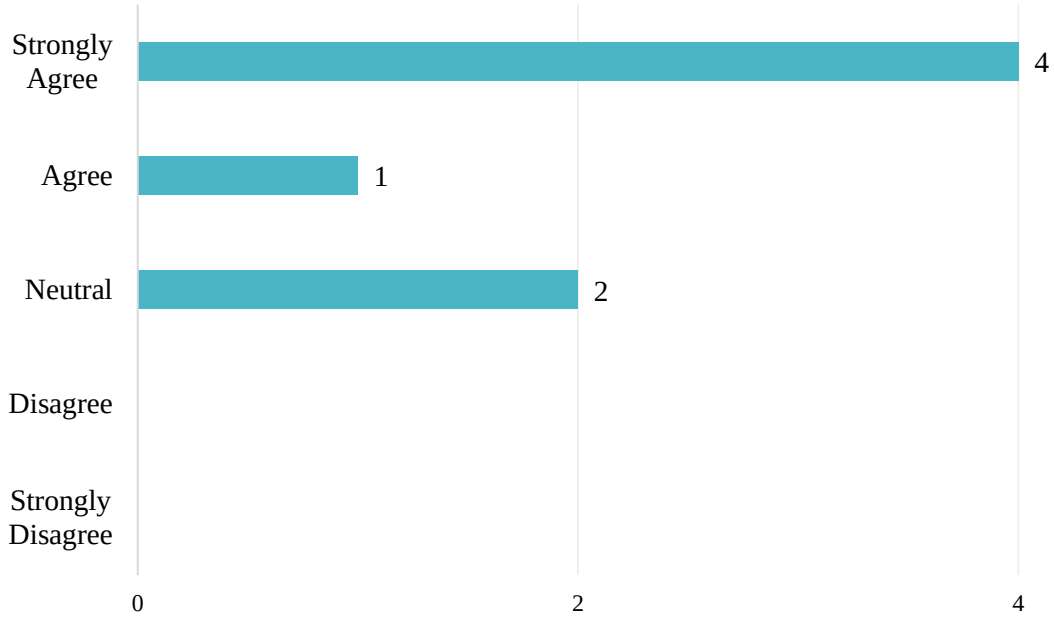

Fig. 4.12. The representation of the perceptions of the regulatory professionals on their agreement or disagreement that regulatory differences between countries have a significant impact on the development/clinical use of monoclonal antibodies.

5 among the 7 regulatory professionals (71.42%) were in favour of the statement that regulatory differences between countries significantly affect the development/clinical use of monoclonal antibodies, while 2 (28.57%) of the regulatory professionals remained neutral.

4.4. Analysis of the Objective 3: Analysis of the therapeutic use and challenges of monoclonal antibodies from different perspectives of professionals.

4.4.Q1: Do you agree or disagree with the statement that the use of monoclonal antibodies will grow in the future?

All of the respondents were asked whether they believe the use of monoclonal antibodies will grow in the future. The results are shown in Table 4.14 and Figure 4.13.

Table 4.14. The perceptions of respondents on their agreement or disagreement that the use of monoclonal antibodies will grow in the future.

Respondents	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
98 (100%)	51 (52.04%)	40 (40.81%)	6 (6.12%)	1 (1.02%)	-

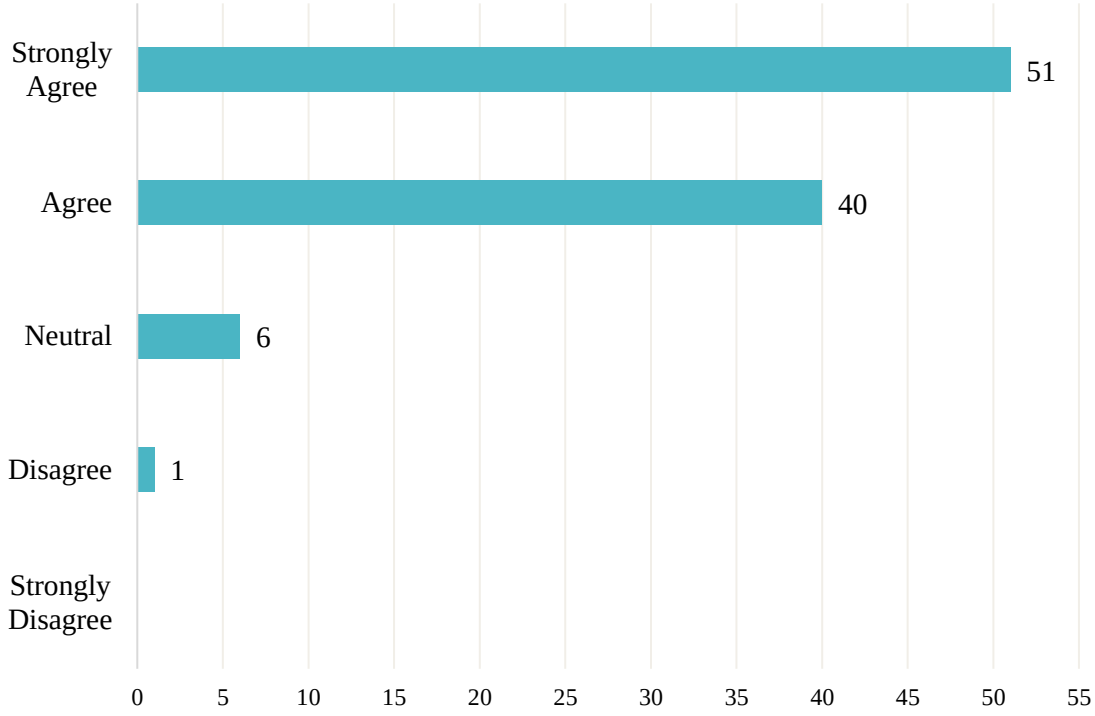

Fig. 4.13. The representation of the perceptives of the respondents on their agreement or disagreement that the use of monoclonal antibodies will grow in the future.

An important number of 91 (92.85%) respondents out of 98, believed that the use of monoclonal antibody will grow in the future, of which 51 of them even strongly agreed. 6 (6.12%) of the respondents remained impartial. One (1.02%) respondent disagreed.

4.4.Q2: I would be very interested to hear from you if you would like to share any additional information, thoughts, or experience of working with monoclonal antibodies.

This question was left optional to answer for participants and aimed to allow volunteer professionals share their experiences, knowledge, and point of views, also, to provide them the opportunity to freely explain their knowledge/point of view according their work experience with monoclonal antibodies. Table 4.15., and Fig. 4.14. show the number of positive perceptions and concerns/challenges about monoclonal antibodies stated by the participated professionals including scientists, medical doctors, regulatory professionals, pharmaceutical/biotechnology professionals.

Table 4.15. The distribution of the positive perceptions and concerns/challenges about monoclonal antibodies defined by the professionals from the associated disciplines.

	Positive Perceptions	**Concerns/ Challenges**	**Total**
Scientists	5 (18.51%)	4 (14.81%)	9 (33.33%)
Medical Doctors	4 (14.81%)	-	4 (14.81%)
Regulatory Professionals	2 (7.40%)	2 (7.40%)	4 (14.81%)
Pharmaceutical/biotechnology professionals	8 (29.62%)	3 (11.11%)	11 (40.74%)
Total	18 (66.66%)	9 (33.33%)	27 (100%)

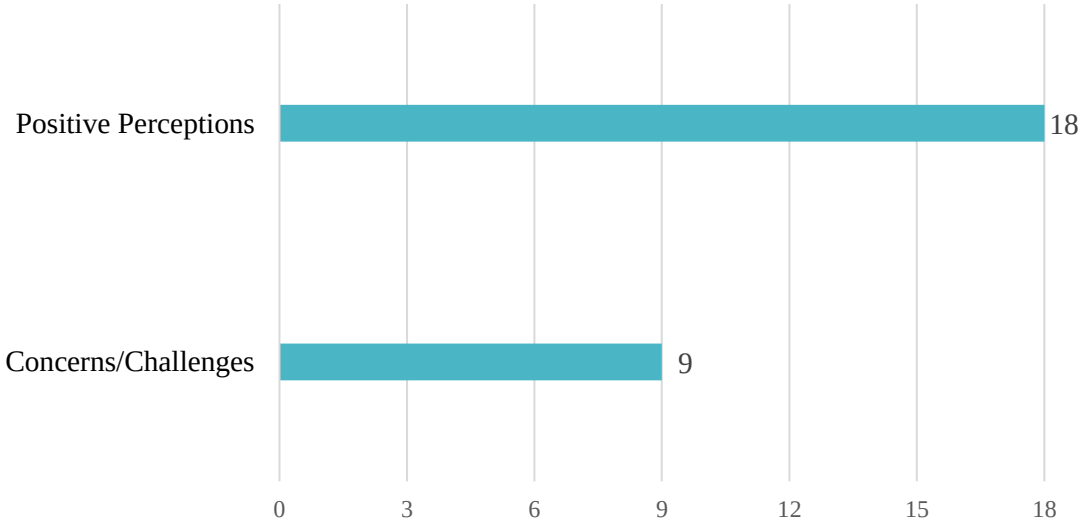

Fig. 4.14. The distribution of the positive perceptions and concerns/challenges about monoclonal antibodies according to the professions of the respondents.

Among the 98 respondents, 27 (27.55%) of them preferred to share additional information, thoughts, or experience of working with monoclonal antibodies. There were 18 (66.66%) positive perceptions and 9 (33.33%) concerns/challenges received among 27 shared knowledge/point of views.

18 responses received from a group of 5 scientists, 4 medical doctors, one regulatory professional and 8 professionals from the pharmaceutical/biotechnology industry. On the other hand, 4 scientists, 2 regulatory professionals and 3 pharmaceutical/biotechnology professionals belonged to the group of 9 respondents who shared their concerns about monoclonal antibodies. The positive perceptions and concerns/challenges about monoclonal antibodies according to scientists is provided in Table 4.16.

Table 4.16. The positive perceptions and concerns/challenges about monoclonal antibodies according to scientists.

Monoclonal Antibody Therapeutics from the Perception of Scientists	
Positive Perceptions (55.55%)	**Concerns/Challenges (44.44%)**
"Monoclonal antibodies have a positive impact. Thus, monoclonal antibodies can be potentially effective to treat the rare disease in the near future."	*"The first clinical trial (that I am aware of) involving mAbs resulted in almost all of the participants dying within days. That makes an impression- mAbs are incredibly powerful but difficult to predict. They're relatively easy to make to produce but risky to actually use."*
"I find the use of biologics and MoAbs to be increasingly necessary in furthering our expertise on how to treat/remedy various ailments, and I feel that their importance in the scientific field will only increase further in the future."	*"The biosimilar market of biologics is still limited because these molecules are complex to produce and difficult to perfectly copy."*
"Armed antibodies in B-cell lymphoma and T-DM1 in breast cancer are really promising."	*"The system for production is limited and needs to be improved. Cell viability is also big concern."*
"I think mAb-based strategies for infectious disease control will grow as a result of COVID-19 pandemic."	*"I have seen some off-target effects in monoclonal antibody therapies in treating cancer which sometimes enhances mortality in patients. More research is definitely needed to explore the field and reduce the off-target effects."*
"*They are beneficial also quite expensive."*	

The positive perceptions in Table 4.16. show that scientists believe monoclonal antibodies are promising for future due to their positive impact on current diseases with no cure, their potential to success in the treatment of rare diseases, as well as their applications

in infectious diseases due to the urgent research focus on COVID-19 pandemic. One of the scientists mentioned high costs as a concern along with his positive response.

As per concerns/challenges, scientists stated that the production system and biosimilar market of monoclonal antibodies are limited due to their complexity, and in certain conditions they can be unpredictable which ends up with mortality.

The positive perceptions and concerns/challenges about monoclonal antibodies according to medical doctors is provided in Table 4.17.

Table 4.17. The positive perceptions about monoclonal antibodies according to medical doctors.

Monoclonal Antibody Therapeutics from the Perception of Medical Doctors
Positive Perceptions (100%)
"Monoclonal Antibodies are very highly emerging and are the future of healthcare. They are the answer to all the diseases that have been deemed impossible to cure up until now. My experience has allowed me to administer monoclonal antibodies and alleviate disease states mainly to do with organ transplantation, particularly of kidneys in patients. I have noticed that they reduced the risk of organ rejection by a relatively high degree. In my experience, they are a boon to me as a healthcare professional and to the patients that I have treated."
"They are the future of the medicine if improved."
"They are the medicines of the future. I think they will be precious especially for the treatment of cancer and autoimmune diseases."
"Excellent molecules but patient access is a concern because of high costs, need biosimilars."

Table 4.17 shows medical doctors agree that monoclonal antibodies can be solution for the currently untreatable diseases, and they encourage the use of monoclonal antibodies. They also believe they will construct the future of the pharmaceutical industry. Even though there is not any concern/challenge stated, one of the medical doctors mentioned patient access as a concern along with her positive response.

The positive perceptions and concerns/challenges about monoclonal antibodies according to regulatory professionals is provided in Table 4.18.

Table 4.18. The positive perceptions and concerns/challenges about monoclonal antibodies according to regulatory professionals.

Monoclonal Antibody Therapeutics from the Perception of Regulatory Professionals	
Positive Perceptions (50%)	**Concerns/Challenges (50%)**
"Regulatory bodies such as US FDA and EMA have well defined regulatory structure for mAbs approval and the approach is same as that of any biotechnological product."	*"Potential safety studies in non-clinical trials are quite limited (only specific species are used) which makes it difficult to evaluate risks for human trials. Overall, more funding is needed for non-clinical development for better results in clinical trials and homogeneity of regulatory framework regarding mAbs are required globally not only in FDA or EMA."*
"Biologics and biosimilar development and to get it approved is really challenging yet promising."	*"ANDA submissions are filed based on the clinical data produced from the randomised, double blinded studies conducted. The challenge mainly included lack of volunteer and patient compliance in the trial."*

According to Table 4.18, distinct regulatory structures by FDA and EMA for marketing approval of biologics/monoclonal antibodies, as well as the promising future of biological products were among positive perceptions. However, one respondent stated that that these regulatory procedures would be a bottleneck if they are not standardized globally. The limitations within pre-clinical and clinical studies were mentioned as other concerns due to lacking in subjects/volunteers and patient compliance.

The positive perceptions and concerns/challenges about monoclonal antibodies according to pharmaceutical/biotechnology professionals is provided in Table 4.19.

Table 4.19. The positive perceptions and concerns/challenges about monoclonal antibodies according to pharmaceutical/biotechnology professionals.

Monoclonal Antibody Therapeutics from the Perception of Pharmaceutical/Biotechnology Professionals	
Positive Perceptions (72.72%)	**Concerns/Challenges (27.27%)**
"I believe the use of solid-phase synthesis for mass-production of Fabs and Fab-drug-conjugates will massively reduce price, giving industry a competitive advantage to scale-up production - business model will shift to high-volume production, at much more affordable prices for patients and insurers. Expect this change in the next 5 years. Added bonus - less risk from bio-contamination since this is essentially chemical synthesis."	*"Large corporations are far too risk-averse in this space. Industry needs to innovate in the basic manufacturing technology, to reduce costs, pass benefits on to patients, and consequently gain market share and boost profits in the long-term. Single-use bioreactors are already helping here, enabling rapid re-purposing, and simplifying validation and cleaning. Similar big-picture thinking is needed".*
"The development of new Automated Technologies for Formulation, and especially for long-term Stability Testing would massively improve/simplify this aspect of antibody development, which is currently very tedious and labour-intensive (even if only one to two technicians work on this per product, it can be all-consuming and involve late-nights/weekends, every day, spanning months to years - which is draining and demotivating. Clear opportunity for innovation to improve working conditions.)"	*"Need new regulatory and technical guidance to avoid/screen for cytokine storms. (e.g. IL-6 driven over-inflammation). (Ref: TGN1412 disaster)."*
"The antibody discovery industry is dynamic and exciting. There seems to be abundant growth for market opportunity and the advanced technology is incredibly innovative!"	*"Stability is a concern, need improvement of technology to stabilize molecular structure."*

"It is very useful in treatment of various diseases and are obtained from the mice plasma that can be later biotechnologically developed for its therapeutic purpose."	
"As biopharmaceutical companies are coming up with biosimilar alternatives, the final cost will eventually be reduced in future."	
"MAbs will be the future treatment predominantly."	
"Use of Phage Display (directed evolution) is already revolutionising the basic discovery of these medicines."	
"I am expecting that it will continue to grow and reach its peak point in the near future. Then, a more feasible therapeutic/therapeutic generation technique (such as CAR-Ts and m-RNA based therapeutics) will substitute their dominancy in the market."	

In addition to the statistics received within the Table 4.6 about the high pricing of monoclonal antibody therapeutics from the Question 4.3.Q2., high costs of monoclonal antibodies are emphasized once again by scientists and medical doctors within the Table 4.16, and Table 4.17. However, there is a positive perception from one of the pharmaceutical/biotechnology professional in the Table 4.19, recommending that if monoclonal antibodies could be produced on a larger scale with advanced manufacturing technologies, hopefully in the upcoming 5 years, it would be a hope for monoclonal antibody therapeutics to reduce the price. Additionally, the respondent stated that advancements in the future technologies may reduce the biocontamination risk as well. Another professional also specified the approach of developing biosimilar alternatives of monoclonal antibody therapeutics could be another opportunity for cost reduction.

One of the respondents also referred to TGN1412 disaster as part of his concern about limited technical guidance from regulatory agencies, contrary to a positive perception stated by a regulatory professional in the Table 4.18.

4.5. Analysis of the Objective 4: Evaluation of the potential of monoclonal antibodies for the treatment of recently emerged COVID-19 pandemic.

According to the optimistic clinical trial outcomes provided within the Chapter II, monoclonal antibodies show hope for the patients who suffer with COVID-19. The lowered need of intensive care unit, ventilation support, reduced death rate among infected patients in several clinical trials supports the view. Another benefit is that they are currently being investigated in all over the world with an extensive focus, which would inevitably improve the findings in much shorter time. Furthermore, their biochemical characteristics that would shorten the defence time against virus, as well as the advantage to be generated in a much shorter time than vaccines are added as extra benefits, as time is very critical in this case, in order to prevent the spread of the virus among nations.

CHAPTER V: DISCUSSION OF THE DATA ANALYSIS

This chapter will discuss the key findings from the data analysis with regard to the fulfilment of research objectives of the study.

The first objective of this study intended to evaluate the progression of the antibody generation techniques over time for better quality, efficacy, and safety of medicines thus to advance their therapeutic use. According to Figure 2.5., the pharmaceutical industry has seen a massive growth in the market value with the discovery of monoclonal antibodies and advancements in the generation of human-similar and human monoclonal antibody types. The growth of monoclonal antibodies has progressed in fast pace because of huge research and development investments due to their promising profile, especially for untreated severe diseases. The statistics of the approved monoclonal antibody formats in the first and the second half of the last 10 years show an impressive difference in a positive way, and ensures that it will continue to grow even much faster, especially with the developments in the genetic engineering methods such as transgenic mice technology (Figure 2.7.) and bispecific monoclonal antibodies (Figure 2.8.) which provide more efficient production and use of monoclonal antibodies.

The purpose of the second objective was to identify the current challenges in the development of monoclonal antibody therapeutics. According to Table 4.5., scientists and pharmaceutical/biotechnology professionals 81.42% agreed that drug design and formulation is the key element that influence on the development of monoclonal antibodies. The drug design and formulation is the very first stage of developing monoclonal antibodies. For this reason, drug development is a critical step as all of the further steps are depending on it, and any mistake made at this stage can impact on the whole process. The results indicate that there are still gaps by means of managing the molecular attributes of monoclonal antibodies to be used for therapeutic purposes, therefore, more research and development studies in the field is needed.

The following two concerns regarding the development were the biodistribution of the molecule with 75.71% agreement, and undesirable by products generated during manufacture and processing with 71.42% agreement. Because they are biological products, both of the biodistribution and manufacturing procedures are dependent to many other

metabolic components in the environment which leads to a quite complex procedure overall, also difficulties in the prediction of the molecules.

According to the results in Table 4.9., 85.71% of the medical doctors agreed that monoclonal antibodies are safe to use, while 67.14% of the scientists and pharmaceutical/biotechnology professionals together formerly stated that there are still uncertainties remaining about the safety of monoclonal antibody therapeutics. This conflict may have occurred because of the difference of their working areas, as scientists are more involved with the research and development, which means a great amount of attempt and failure until success, while medical doctors on the other hand, prescribe the already authorized monoclonal antibodies which had been tested for numerous times until their safety, quality and efficacy are approved and risk/benefit balance is found reasonable.

When the effectiveness of monoclonal antibodies is evaluated as newly developed treatment for diseases on a molecular scale by scientists, the 68.88% scientists agree that monoclonal antibodies work well as a newly developed treatment, while from the medical doctor's point of view, they are found 85.71% effective. The statistics indicate that monoclonal antibodies show satisfactory outcomes in both research and development and medical use.

Furthermore, among the same group of 66 respondent which consists of scientists and medical doctors, 68.18% believed that the benefits of monoclonal antibodies outweigh the risks, which shows that scientists and medical doctors are both hopeful for monoclonal antibody therapeutics. Additionally, it is another evidence that they are well worth to further investigate, and to unravel the existing gaps.

Results show that the obtained responses regarding the high costs of monoclonal antibodies are in parallel with the findings of secondary research, with agreement of 60.20% of the total respondents. Even though the majority of the respondents stated that there are several governmental funding/support in their country, the specified funding for the research and development were comprehensive of all scientific fields, and not specific to monoclonal antibodies. There are a few monoclonal antibody therapeutics for the treatment of autoimmune disorders and for several cancer types that Turkish Social Security Institution (SGK) supports their use. Nevertheless, their supply to pharmacies are limited, and some of them are only partially funded (TEB, 2018; SGK, 2018).

Even though the regulatory approval procedures of monoclonal antibody therapeutics are highly time consuming and consist of many measures and requirements, they are entirely focused on the public safety and they cannot be avoided by the pharmaceutical industry. According to the outcomes of the Figure 4.11, the national regulatory agencies are deemed adequate enough to ensure product efficacy, quality, and patient safety by respondents from the USA, Ireland, and India with 71.42% agreement which is a considerably satisfactory result overall.

On the other hand, the same percentage of regulatory professionals also agreed that the regulatory differences between countries significantly affect the development/clinical use of monoclonal antibodies. Supporting that, as part of the third objective, one of the regulatory professionals stated in Table 4.18 that there should be only a single regulatory framework which should be adopted globally. This is a significant gap in the global regulatory perspective of monoclonal antibody development. To be more specific, if all countries had implemented the same regulations, the pharmacovigilance tracking would be much easier, and there would be more knowledge available about the use of monoclonal antibodies such as the age group or the disease type that it is used for. Additionally, it would also reduce the time for various procedures such as market approval, which would also ease the approval of biosimilar alternatives that play a key role in cost reduction.

With the third objective, different perspectives of professionals were aimed to be analysed regarding the therapeutic use and challenges of monoclonal antibody therapeutics with a qualitative approach. When the received points of views are compared individually among professionals, medical doctors had the highest (100%) percentage of positive perceptions in the Table 4.17, which is relatively predictable, as it was formerly mentioned medical professionals are more involved with the approved therapeutics, therefore, they are less exposed to the relatively negative aspects of the molecules.

Moreover, high costs were the most mentioned concern of the total respondents once again. The considerations shared by pharmaceutical/biotechnology professionals in the Table 4.19 such as biosimilar alternatives, and future advancements in the manufacturing technology will be the first steps to overcome those bottlenecks in the development and therapeutic use of monoclonal antibodies, especially to minimize cost. In addition to that, it is stated in the Table 4.19 that scale-up manufacturing can reduce prices and the

biocontamination risk at the same time. This future improvement would also respond to the challenge of undesired by products during manufacturing.

Although there were concerns about the safety and high costs of monoclonal antibodies, as well as bottlenecks in the manufacturing due to various factors, the 92.85% of the total respondents who agreed that monoclonal antibodies will grow in the future (Table 4.14), is a great indication that scientists, medical doctors, regulatory professionals and pharmaceutical/biotechnology professionals believe that these challenges are achievable and will not prevent the growth of monoclonal antibody therapeutics.

The final objective sought to evaluate their potential for the treatment of COVID-19 that has recently emerged pandemic. With the ongoing studies and extreme current focus on the pandemic worldwide, the research and development in this field have already gained a massive speed. In Table 4.16 a very spot-on comment was made by a scientist, stating that the research and development of monoclonal antibodies especially for infectious diseases will rapidly grow in the near future as a result of COVID-19 pandemic.

According to the clinical trial results presented in Chapter II, death toll and need for intensive care unit among COVID-19 patients were decreased following the exposure to tocilizumab which is an excellent progress. Additionally, the 92-year-old man after the treatment with levilimab is a great hope for elder patients who are being affected by the virus more than any other age group. The advantage of monoclonal antibodies is that they are approved therapeutics which have already been used against cytokine storms which are present in COVID-19 patients as well. Along with the hopeful outcomes from the ongoing clinical trials, and the shorter time needed for developing monoclonal antibodies compared to vaccines, as well as their biochemical aspects, monoclonal antibodies show a great promise for the treatment of COVID-19.

CHAPTER VI: CONCLUSIONS AND RECOMMENDATIONS

6.1. Research Conclusions

- The monoclonal antibody discovery has reshaped the research and development focus and growth of the pharmaceutical industry with its promising profile for currently untreatable diseases, and excessive market demand.
- The chimerization technology in the generation of monoclonal antibodies helped to reduce the safety risks. However, more advanced technologies such as humanization of the monoclonal antibodies sourced from different species, or generation of human monoclonal antibodies provided a safer use.
- Implementation of the genetic engineering techniques into monoclonal antibodies (i.e. bispecific monoclonal antibodies) fostered the efficacy of the mechanism of action. These efforts to generate more human-like, or effective monoclonal antibodies also improved the quality of the product.
- Drug design and formulation is the most challenging factor in the development of monoclonal antibodies, due to the complexity of the molecule. Besides bringing the challenges in the production of monoclonal antibodies, molecular instability can put human health at risk, even may result in mortality.
- The current technology has not been improved enough to perform a standardized mass manufacturing of monoclonal antibodies, resulting in high costs in the production.
- Regulatory differences between countries is a challenge for the advancements in monoclonal antibody therapeutics.
- Monoclonal antibodies show a great hope for many diseases that are currently untreatable, and have an extraordinary potential to shape the future of the pharmaceutical industry.
- The ongoing pre-clinical and clinical trials show that monoclonal antibodies have a high potential to overcome the recently emerged COVID-19 pandemic.

6.2. Strategic Conclusions

- Considering the influential aspects of the monoclonal antibodies within the pharmaceutical market profiles, and the rich product pipeline they provide,

monoclonal antibodies are well worth to invest in as there are still gaps remaining about the biochemical aspects of monoclonal antibodies.

- The advancements in the formulation of monoclonal antibodies and implementation of genetic engineering techniques are likely reduce the safety risks, while increasing the efficiency and quality.
- As experts in this field, the professionals from the pharmaceutical/biotechnology industry, scientists, medical doctors, and regulatory professionals are well-aware of the risks and challenges that monoclonal antibodies bring. However, they still believe that the monoclonal antibodies will shape the future of the pharmaceutical industry, which indicates that aforementioned challenges are likely to be manageable in the near future.
- Considering that the availability and effectiveness that monoclonal antibodies show in the short-term, they can be very helpful for the patients who are currently suffering with COVID-19, especially the ones who are being treated in intensive care unit.
- Monoclonal antibodies in the COVID-19 treatment is likely to reduce the time needed for the treatment, which is precious at the moment. Thus, it can prevent the virus to spread and infect more people.

6.3. Recommendations

- The studies on the implementation of high-volume manufacturing technologies into monoclonal antibodies should be fostered to reduce the manufacturing costs. These technology will also help to decrease biocontamination risks, which answers the challenge of undesired by products during manufacturing of monoclonal antibodies.
- The pharmaceutical industry should consistently follow the patent expirations and focus on producing biosimilar alternatives to reduce high costs.
- Governmental supports/funding should be enhanced. Even though there are several funding agencies, most of them encourage general scientific research instead of research studies specific to monoclonal antibodies (except for unexpected conditions such as COVID-19.)
- The regulations for biological products should be globally standardized.
- As monoclonal antibodies are promising for the COVID-19 pandemic with both of their biochemical mechanism as well as their aspect to take action in a much shorter

term than vaccines, special attention and focus must be provided for the research and development studies of monoclonal antibodies as the treatment for COVID-19 is urgently needed.

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8. APPENDICES

Appendix A. The list of monoclonal antibody drugs that approved by major agencies from 1986 to 2013 (Strohl, 2014).

US Trade Name (generic name)	Company	Target	Source of Domains	Antibody Format	Primary Indication	Approval Year (US)
Orthoclone OKT3® (muromonab-CD3)	Ortho Biotech (J&J)	CD3	Mouse	Mouse IgG2a	OTR	1986; WD 2011
ReoPro® (abciximab)	Centocor (J&J) / Lilly	gPIIb /IIIa	Mouse	Chimeric Fab derived from IgG1	CVD	1994
Rituxan® (rituximab)	Biogen/Idec/ Genentech	CD20	Mouse	Chimeric IgG1n	NHL, RA	1997
Zenapax® (daclizumab)	Abbott (PDL/Roche)	CD25	Mouse	Humanized IgG1	OTR	1997
Remicade® (infliximab)	Centocor (now J&J)	TNF-a	Mouse	Chimeric IgG1n	Crohn's disease, RA	1998
Synagis® (palivizumab)	MedImmune	RSV F-protein	Mouse	Humanized IgG1n	RSV (infant)	1998
Herceptin® (trastuzumab)	Genentech	HER2	Mouse	Humanized IgG1n	Breast cancer	1998
Simulect® (basiliximab)	Novartis	CD25	Mouse	Chimeric IgG1n	OTR	1998
Mylotarg® (gemtuzumab ozogamicin)	Wyeth	CD33	Mouse	Humanized IgG4n-Ozogamicin conjugate	Leukemia	2000; WD 2010
Campath -1H® (alemtuzumab)	Genzyme	CD52	Mouse	Humanized IgG1n	Leukemia	2001; WD 2012
Zevalin® (ibritumomab tiuxetan)	Biogen/Idec	CD20	Mouse	Murine IgG1n conjugate, Y-90 or In-111	NHL	2002
Humira® (adalimumab)	CAT, Abbott	TNF-a	Human phage display library	Human IgG1n	RA, Crohn's disease	2002
Xolair® (omalizumab)	Genentech	IgE	Mouse	Humanized IgG1n	Asthma	2003
Bexxar® (tositumomab-I131)	Corixa	CD20	Mouse	Murine IgG2a/ Z-I-131	NHL	2003
Raptiva® (efalizumab)	Genentech	CD11a	Mouse	Humanized IgG1n	Psoriasis	2003; WD 2009
Erbitux® (cetuximab)	ImClone / BMS	EGF-R	Mouse	Chimeric IgG1n	Colorectal cancer	2004

Avastin® (bevacizumab)	Genentech	VEGF	Mouse	Humanized IgG1	Colorectal cancer	2004
Tysabri® (natalizumab)	Biogen/Elan	a4 of a4þ1/7	Mouse	Humanized IgG4n	Multiple sclerosis	2004
Lucentis® (ranibizumab)	Genentech / Novartis	VEGF-A	Mouse	Humanized IgG1n Fab domain	Wet AMD	2006
Vectibix® (panitumumab)	Amgen	EGF-R	Transgenic mouse producing human antibodies	Human IgG2n	Colorectal cancer	2006
Soliris® (eculizumab)	Alexion Pharma	C5	Mouse	Humanized IgG2/4 hybrid	PNH (reduce hemolysis)	2007
Simponi® (golimumab)	J&J	TNF-a	Transgenic mouse producing human antibodies	Human IgG1	RA	2009
Stelara® (ustekinumab)	J&J	p40 (IL-12 & IL- 23)	Transgenic mouse producing human antibodies	Human IgG1	Psoriasis	2009
Removab® (catumaxomab)	Fresenius / Trion	EpCAM, CD3	Rat (one Fab arm); mouse (other Fab arm)	Rat IgG2b-mouse IgG2a hybrid IgG	Malignant ascites; Cancer	2009 (EU only)
Cimzia® (certolizumab pe-gol)	UCB / Schwartz	TNF-a	Mouse	PEGylated humanized Fab domain	RA	2009
Ilaris® (canakinumab)	Novartis	IL-1þ	Transgenic mouse producing human antibodies	Human IgG1k	CAPS	2009
Arzerra® (ofatumumab)	GenMab / GSK	CD20	Transgenic mouse producing human antibodies	Human IgG1k	CLL	2009
Actemra®; (tocilizumab)	Roche / Chugai	IL-6R	Mouse	Humanized IgG1	Castlemans disease; RA	2010

Prolia® and Xgeva® (denosumab)	Amgen / GSK	RANK-L	Transgenic mouse producing human antibodies	Human IgG2	Osteoporosis; bone cancer	2010
Benlysta® (belimumab)	GSK / HGS	BLyS	Human phage display library	Human IgG1Z	Lupus (SLE)	2011
Yervoy® (ipilimumab)	Medarex / BMS	CTLA4	Transgenic mouse producing human antibodies	Human IgG1k	Malignant melanoma	2011
Adcetris® (brentuximab vedotin)	Seattle Genetics/ Takeda/ Millenium	CD30	Mouse	Chimeric IgG1 conjugated NP-toxin	Hodgkin lymphoma	2011
Poteligeo® (mogamulizu-mab)	Kyowa Hakko Kirin	CCR4	Mouse	Humanized low-fucose IgG1	ATL	2012 (Japan only)
Perjeta® (pertuzumab)	Genentech	Her2	Mouse	Humanized IgG1	Breast cancer	2012
Abthrax (raxibacumab)	GSK / HGS	*Bacillus anthracis* PA toxin	Human phage display library	Human IgG1	Anthrax biodefense	2012
Kadcyla (trastuzumab emtansine)	Genentech / Immunogen	Her2	Mouse	Humanized IgG1-ADC (conjugated to DM1; maytansanoid)	Breast cancer	2013

Appendix B. The list of monoclonal antibody drugs that approved by FDA from 2013 to 2019 (Lu *et al.*, 2020).

Monoclonal Antibody	Brand name	Company	Target	Format	Technology	Primary Indication	Approval Year (US)
Obinutuzumab	Gazyva, Gazyvaro	Biogen Inc./Roche, F. Hoffmann-La Roche, Ltd./Genentech Inc.	CD20	Humanized IgG1 Glycoengineered	Hybridoma	Chronic lymphocytic leukemia	2013
Siltuximab	Sylvant	Centocor Inc./Janssen Biotech Inc./ Janssen-Cilag International NV	IL-6	Chimeric IgG1	Hybridoma	Castleman disease	2014
Ramucirumab	Cyramza	Eli Lilly/ImClone Systems Inc.	VEGFR 2	Human IgG1	Phage display	Gastric cancer	2014
Vedolizumab	Entyvio	Genentech Inc./Millennium Pharmaceuticals Inc./Takeda Pharmaceuticals U.S.A. Inc.	α4β7 integrin	Humanized IgG1	Hybridoma	Ulcerative colitis, Crohn disease	2014
Blinatumomab	Blincyto	Amgen	CD19, CD3	Murine bispecific tandem scFv	Hybridoma	Acute lymphoblastic leukemia	2014
Nivolumab	Opdivo	Bristol-Myers Squibb/Ono Pharmaceutical Co., Ltd.	PD-1	Human IgG4	Transgenic mice	Melanoma, non-small cell lung cancer	2014
Pembrolizumab	Keytruda	Merck & Co. Inc.	PD-1	Humanized IgG4	Hybridoma	Melanoma	2014
Idarucizumab	Praxbind	Boehringer Ingelheim Pharmaceuticals	Dabigatran	Humanized Fab	Hybridoma	Reversal of dabigatran-induced anticoagulation	2015
Necitumumab	Portrazza	Eli Lilly/ImClone Systems Inc.	EGFR	Human IgG1	Phage display	Non-small cell lung cancer	2015
Dinutuximab	Unituxin	United Therapeutics Corporation	GD2	Chimeric IgG1	Hybridoma	Neuroblastoma	2015
Secukinumab	Cosentyx	Novartis Pharmaceuticals Corp.	IL-17α	Human IgG1	Transgenic mice	Psoriasis	2015
Mepolizumab	Nucala	Centocor Inc./GlaxoSmith Kline	IL-5	Humanized IgG1	Hybridoma	Severe eosinophilic asthma	2015
Alirocumab	Praluent	Regeneron Pharmaceuticals Inc./ Sanofi.	PCSK9	Human IgG1	Transgenic mice	High cholesterol	2015
Evolocumab	Repatha	Amgen/Amgen Astellas BioPharma K.K.	PCSK9	Human IgG2	Transgenic mice	High cholesterol	2015

Daratumumab	Darzalex	Genmab A/S/Janssen Biotech Inc.	CD38	Human IgG1	Transgenic mice	Multiple myeloma	2015
Elotuzumab	Empliciti	Bristol-Myers Squibb/AbbVie Inc.	SLAMF 7	Humanized IgG1	Hybridoma	Multiple myeloma	2015
Ixekizumab	Taltz	Eli Lilly	IL-17α	Humanized IgG4	Hybridoma	Psoriasis	2016
Reslizumab	Cinqaero, Cinqair	Celltech, UCB/Schering-Plough/Teva Pharmaceutical Industries, Ltd.	IL-5	Humanized IgG4	Hybridoma	Asthma	2016
Olaratumab	Lartruvo	Eli Lilly/ImClone Systems Inc.	PDGFR α	Human IgG1	Transgenic mice	Soft tissue sarcoma	2016
Bezlotoxumab	Zinplava	Merck & Co. Inc.	*Clostridium difficile* enterotoxin B	Human IgG1	Transgenic mice	Prevention of *Clostridium difficile* infection recurrence	2016
Atezolizumab	Tecentriq	Roche, F. Hoffmann-La Roche, Ltd./ Genentech Inc.	PD-L1	Humanized IgG1	Hybridoma	Bladder cancer	2016
Obiltoxaximab	Anthim	Elusys Therapeutics Inc.	*B. anthrasis*	Chimeric IgG1	Hybridoma	Prevention of inhalational anthrax	2016
Inotuzumab ozogamicin	Besponsa	Wyeth Pharmaceuticals /Pfizer.	CD22	Humanized IgG4	Hybridoma	Acute lymphoblastic leukemia	2017
Brodalumab	Siliq, Lumicef	MedImmune/Amgen/Kyowa Hakko Kirin /AstraZeneca/Valeant Pharmaceuticals International Inc.	IL-17R	Human IgG2	Transgenic mice	Plaque psoriasis	2017
Guselkumab	Tremfya	MorphoSys/Janssen Biotech Inc.	IL-23 p19	Human IgG1	Phage display	Plaque psoriasis	2017
Dupilumab	Dupixent	Regeneron Pharmaceuticals Inc./ Sanofi	IL-4Rα	Human IgG4	Transgenic mice	Atopic dermatitis	2017
Sarilumab	Kevzara	Regeneron Pharmaceuticals Inc./ Sanofi	IL-6R	Human IgG1	Transgenic mice	Rheumatoid arthritis	2017

Avelumab	Bavencio	Merck Serono International S.A./ Pfizer	PD-L1	Human IgG1	Phage display	Merkel cell carcinoma	2017
Ocrelizumab	Ocrevus	Biogen Inc./Roche, F. Hoffmann-La Roche, Ltd./Genentech Inc./SIGMA-TAU Industrie Farmaceutiche Riu- nite S.p.A.	CD20	Humanized IgG1	Hybridoma	Multiple sclerosis	2017
Emicizumab	Hemlibra	Chugai Pharmaceutical Co., Ltd./ Roche, F. Hoffmann-La Roche, Ltd.	Factor IXa, X	Humanized IgG4, bispecific	Hybridoma	Hemophilia A	2017
Benralizumab	Fasenra	MedImmune/Kyowa Hakko Kirin/ AstraZeneca	IL-5Rα	Humanized IgG1	Hybridoma	Asthma	2017
Gemtuzumab ozogamicin	Mylotarg	Pfizer	CD33	Humanized IgG4; ADC	Hybridoma	Acute myeloid leukemia	2017
Durvalumab	Imfinzi	MedImmune/AstraZeneca	PD-L1	Human IgG1	Transgenic mice	Bladder cancer	2017
Burosumab	Crysvita	Kyowa Hakko Kirin/Ultragenyx Pharmaceutical Inc.	FGF23	Human IgG1	Transgenic mice	X-linked hypophosphatemia	2018
Lanadelumab	Takhzyro	Dyax Corp.	Plasma kallikrein	Human IgG1	Phage display	Hereditary angioedema attacks	2018
Mogamulizumab	Poteligeo	Kyowa Hakko Kirin	CCR4	Humanized IgG1	Hybridoma	Mycosis fungoides or Sézary syndrome	2018
Erenumab	Aimovig	Novartis	CGRPR	Human IgG2	Transgenic mice	Migraine prevention	2018

Galcanezumab	Emgality	Eli Lilly	CGRP	Humanized IgG4	Hybridoma	Migraine prevention	2018
Tildrakizumab	Ilumya	Merck & Co. Inc./Sun Pharmaceutical Industries, Ltd.	IL-23 p19	Humanized IgG1	Hybridoma	Plaque psoriasis	2018
Cemiplimab	Libtayo	Regeneron Pharmaceuticals Inc.	PD-1	Human mAb	Transgenic mice	Cutaneous squamous cell carcinoma	2018
Emapalumab	Gamifant	NovImmmune	IFNγ	Human IgG1	Phage display	Primary hemophagocytic lymphohistiocytosis	2018
Fremanezumab	Ajovy	Teva Pharmaceutical Industries, Ltd.	CGRP	Humanized IgG2	Hybridoma	Migraine prevention	2018
Ibalizumab	Trogarzo	Taimed Biologics Inc./ Theratechnologies Inc.	CD4	Humanized IgG4	Hybridoma	HIV infection	2018
Moxetumomab pasudodox	Lumoxiti	MedImmune/AstraZeneca	CD22	Murine IgG1 dsFv	Phage display	Hairy cell leukemia	2018
Ravulizumab	Ultomiris	Alexion Pharmaceuticals Inc.	C5	Humanized IgG2/4	Hybridoma	Paroxysmal nocturnal hemoglobinuria	2018
Caplacizumab	Cablivi	Ablynx	von Willebrand factor	Humanized Nanobody	Hybridoma	Acquired thrombotic thrombocytopenic purpura	2019
Romosozumab	Evenity	Amgen/UCB	Sclerostin	Humanized IgG2	Hybridoma	Osteoporosis in postmenopausal women at increased risk of fracture	2019
Risankizumab	Skyrizi	Boehringer Ingelheim Pharmaceuticals / AbbVie Inc.	IL-23 p19	Humanized IgG1	Hybridoma	Plaque psoriasis	2019

Polatuzumab vedotin	Polivy	Roche, F. Hoffmann-La Roche, Ltd.	CD79β	Humanized IgG1 ADC	Hybridoma	Diffuse large B-cell lymphoma	2019
Brolucizumab	Beovu	Novartis Pharmaceuticals Corp.	VEGF-A	Humanized scFv	Hybridoma	Macular degeneration	2019
Crizanlizumab	Adakveo	Novartis Pharmaceuticals Corp.	P-selectin	Humanized IgG2	Hybridoma	Sickle cell disease	2019

Appendix C. A sample of the consent form that was provided to all respondents before their participation to the questionnaire.

QUESTIONNAIRE

This questionnaire is carried out by a student at Griffith College Dublin to identify the current challenges in the development and therapeutic use of monoclonal antibodies as promising agents in the pharmaceutical industry.

This is an online questionnaire that will take approximately 4-7 minutes. Your participation in this research study is voluntary.

We will keep your personal data confidential, and the outcomes of this research will be used for scholarly purposes only. The name and surname are asked only to ensure the information we receive is sourced by experts in the field as this is scientific research and appeals only to specific professionals in the biotechnology, pharmaceutical, and health care industries.

Your identification and responses will not be shared with the public.

Thank you very much for your time and participation.

Appendix D. A sample of the Section A of the questionnaire that was carried out with scientists, medical doctors, regulatory professionals, pharmaceutical/biotechnology professionals.

SECTION A

Name: _____

Surname: _____

1. **Please describe your level of education.**

   Please tick ✓ the appropriate answer:

   ☐ Certificate/Diploma

   ☐ Bachelor's degree/Advanced diploma

   ☐ Master's degree

   ☐ PhD degree

   ☐ Other level (please specify) _____

2. **Please describe your profession and area of specialty:**

   _____

3. **Years of experience** _____

Appendix E. A sample of the Section B of the questionnaire that was carried out with scientists.

SECTION B

SCIENTISTS

Please tick the appropriate answer for each question below.

1. **Do you have any involvement/experience/knowledge in the research and development and/or production of monoclonal antibodies?**

   ☐ Yes
   ☐ No
   ☐ Other, please kindly clarify in your own words:

   _____

   _____

2. **Do you agree or disagree with the statement that monoclonal antibodies are effective as a newly developed treatment for diseases?**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree
   ☐ Other, please kindly clarify in your own words:

   _____

   _____

3. **Do you agree or disagree with the statement that the benefits of monoclonal antibodies outweigh the risks?**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree

4. **Do you agree that there are certain factors can influence the development process of monoclonal antibodies:**

   i. **Challenges in drug design and formulation**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree
   ☐ N/A

   ii. **Challenges in chemical structure**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree
   ☐ N/A

   iii. **Undesirable by products generated during manufacture and processing**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree
   ☐ N/A

   iv. **Uncertainties about the safety of monoclonal antibody therapeutics**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree
   ☐ N/A

v. **Insufficient knowledge about the effectiveness of monoclonal antibody therapeutics**

☐ Strongly agree
☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree
☐ N/A

vi. **Challenges in biodistribution of the molecule**

☐ Strongly agree
☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree
☐ N/A

5. **Is there any governmental research funding/support in your country for the development of biologics/monoclonal antibodies?**

☐ Yes, please kindly specify your country and the type of governmental funding/support:

_____

_____

☐ No
☐ Other, please kindly clarify in your own words:

_____

_____

6. **Do you agree or disagree with the statement that monoclonal antibodies are overpriced?**

☐ Strongly agree
☐ Agree
☐ Neutral

☐ Disagree
☐ Strongly disagree

7. **Do you agree or disagree with the statement that the use of monoclonal antibodies will grow in the future?**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree

8. **I would be very interested to hear from you if you would like to share any additional information, thoughts, or experience of working with biologics/monoclonal antibodies:**

Appendix F. A sample of the Section B of the questionnaire that was carried out with medical doctors.

SECTION B

MEDICAL DOCTORS

Please tick the appropriate box for each question below.

1. **Do you have any experience of treating your patients with monoclonal antibodies?**

   ☐ Yes, please kindly specify the name of the disease and the type of monoclonal antibodies you have prescribed:

   _____

   _____

   ☐ No

   ☐ Other, please kindly clarify in your own words:

   _____

   _____

2. **Do you agree or disagree with the statement that monoclonal antibodies are safe to use?**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree

3. **Do you agree or disagree with the statement that monoclonal antibodies are effective as a newly developed treatment for diseases?**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree

4. **Do you agree or disagree with the statement that the benefits of monoclonal antibodies outweigh the risks?**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree

5. **Do you agree or disagree with the statement that monoclonal antibodies are overpriced?**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree

6. **Is there any governmental support (i.e. medical card, medical allowance) in your country for the use of biologics/monoclonal antibodies?**

   ☐ Yes, please kindly specify your country and the type of governmental support:

   _____

   _____

   ☐ No
   ☐ Other, please kindly clarify in your own words:

   _____

   _____

7. **Do you agree or disagree with the statement that the use of monoclonal antibodies will grow in the future?**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree

☐ Strongly disagree

8. **I would be very interested to hear from you if you would like to share any additional information, thoughts, or experience of working with biologics/monoclonal antibodies:**

Appendix G. A sample of the Section B of the questionnaire that was carried out with regulatory professionals.

SECTION B

REGULATORY PROFESSIONALS

Please tick the appropriate box for each question below.

1. **Do you have any involvement/experience/knowledge in regulatory affairs for biologics/monoclonal antibodies?**

   ☐ Yes
   ☐ No
   ☐ Other, please kindly clarify in your own words:

   _____

   _____

2. **Do you agree or disagree with the statement that the regulations for biologics/monoclonal antibodies in your country are adequate enough to ensure patient safety, product efficacy and quality? (Please kindly specify your country.)**

   ☐ Strongly agree
   ☐ Agree
   ☐ Neutral
   ☐ Disagree
   ☐ Strongly disagree
   ☐ Other

   Please kindly clarify in your own words:

   _____

   _____

3. **Do you agree or disagree with the statement that regulatory differences between countries have a significant impact on the development/clinical use of monoclonal antibodies?**

   ☐ Strongly agree

☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree
☐ Other, please kindly clarify in your own words:

_____

_____

4. **Do you agree or disagree with the statement that monoclonal antibodies are overpriced?**

☐ Strongly agree
☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree

5. **Is there any governmental research funding/support in your country for development of biologics/monoclonal antibodies?**

☐ Yes, please kindly specify your country and the type of governmental funding/support:

_____

_____

☐ No
☐ Other, please kindly clarify in your own words:

_____

_____

6. **Do you agree or disagree with the statement that the use of monoclonal antibodies will grow in the future?**

☐ Strongly agree
☐ Agree

☐ Neutral
☐ Disagree
☐ Strongly disagree

7. **I would be very interested to hear from you if you would like to share any additional information, thoughts or experience of working with the regulatory approval procedures and associated challenges for biologics/monoclonal antibodies:**

Appendix H. A sample of the Section B of the questionnaire that was carried out with professionals working in the pharmaceutical/biotechnology industry.

SECTION B

PROFESSIONALS WORKING IN THE

PHARMACEUTICAL/BIOTECHNOLOGY INDUSTRY

Please tick the appropriate box for each question below.

1. **Do you have any experience of working with biologics/monoclonal antibodies?**

   ☐ Yes

   ☐ No

   ☐ Other, please kindly clarify in your own words:

   _____

   _____

2. **Do you agree that there are certain factors that can influence the development process of monoclonal antibodies:**

   i. **Challenges in drug design and formulation**

      ☐ Strongly agree
      ☐ Agree
      ☐ Neutral
      ☐ Disagree
      ☐ Strongly disagree
      ☐ N/A

   ii. **Challenges in chemical structure**

      ☐ Strongly agree
      ☐ Agree
      ☐ Neutral
      ☐ Disagree
      ☐ Strongly disagree
      ☐ N/A

iii. Undesirable by products generated during manufacture and processing

☐ Strongly agree
☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree
☐ N/A

iv. Uncertainties about the safety of monoclonal antibody therapeutics

☐ Strongly agree
☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree
☐ N/A

v. Insufficient knowledge about the effectiveness of monoclonal antibody therapeutics

☐ Strongly agree
☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree
☐ N/A

vi. Challenges in biodistribution of the molecule

☐ Strongly agree
☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree
☐ N/A

3. **Is there any governmental research funding/support in your country for the development of biologics/monoclonal antibodies?**

☐ Yes, please kindly specify your country and the type of governmental funding/support:

_____

_____

☐ No
☐ Other, please kindly clarify in your own words:

_____

_____

4. **Do you agree or disagree with the statement that monoclonal antibodies are overpriced?**

☐ Strongly agree
☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree

8. **Do you agree or disagree with the statement that the use of monoclonal antibodies will grow in the future?**

☐ Strongly agree
☐ Agree
☐ Neutral
☐ Disagree
☐ Strongly disagree

5. **I would be very interested to hear from you if you would like to share any additional information, thoughts or experience about monoclonal antibodies:**

_____

_____